European Journal of Surgical Oncology 45 (2019) 446–453

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

D2 lymphadenectomy for gastric cancer as an independent prognostic factor of 10-year overall survival

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ARTICLE INFO

Article history:
Received 9 June 2018
Received in revised form
2 October 2018
Accepted 28 October 2018
Available online 30 October 2018

Keywords:
Gastric cancer
Surgery
Lymphadenectomy
Oncologic outcomes
Survival
Natural history

ABSTRACT

Background: The extension of lymphadenectomy for GA remains on debate even after Eastern and Western clinical trials. The main concern is if morbidity of extended lymphadenectomy could be justified based on benefits in oncologic outcomes. This study addressed the extension of lymphadenectomy as a prognostic factor of overall survival (OS) for gastric adenocarcinoma (GA).
Methods: Consecutive patients who underwent gastrectomy for GA were retrospectively evaluated. Univariate and multivariate models assessed determinants of OS.
Results: From 1994 to 2015, 656 consecutive patients who underwent gastrectomy were evaluated. Briefly, 455 (69.4%) were male, 397 (60.5%) underwent total gastrectomy, Roux-en-Y reconstruction was done in 483 (73.6%), and R0 resection was achieved in 632 patients (96.3%). According to multivariate analysis, the risk of death was increased with older age (≥70-y), high-grade tumors, lesions ≥ 5 cm, positive nodes ≥ 3, and extra-gastric resections. Otherwise, D2 lymphadenectomy improved median OS (37 versus 16 months), 3-y (51.1 versus 32.2%), 5-y (43.2 versus 26), and 10-y OS (30.6 versus 9.4%), with HR of 0.48 (95% CI 0.34–0.67, $p < 0.001$). The general median OS was 31 months and 3-, 5-, and 10-y were 47.6, 40, and 27%, respectively. The median follow-up for all patients was 26 months, and for survivors was 65 months.
Conclusion: This study showed D2 lymphadenectomy for GA as an independent prognostic factor for OS, even after 5-y and until 10-y. Our study suggests that D2 should be offered as the curative-intent treatment for all patients with GA that fit to undergo surgery.

Introduction

Gastric cancer represents the 5th worldwide cancer with estimated 952.000 new cases per year, and it is the 3rd leading cause of death by cancer with approximately 726.000 (8.8%) deaths per year [1]. However, there are geographical disparities between Eastern and Western countries. Twenty-eight thousand new cases and 10.960 deaths were estimated in 2017 in the United States of America [2]. On the other hand, the incidence in Asia achieves 677.000 new cases per year, representing more than 70% of global incidence. Moreover, the highest estimated mortality rates are in Eastern Asia (24 per 100,000 in men, 9.8 per 100,000 in women), which differs from the lowest in Northern America (2.8 and 1.5, respectively) [1]. In Brazil, gastric cancer represents the 4th most incident cancer in men and the 5th in women, with 12.600 and 7.600 estimated new cases in 2016, respectively [3].

The surgical treatment of resectable and non-metastatic gastric cancer is world accepted as the mainstream of curative-intent treatment and should be associated with chemotherapy according to initial stage and vary according to Western versus Eastern countries [4,5]. The depth of tumor invasion, the metastatic LN status, and R0 resection are the most important independent prognostic factors for overall and disease-free survival (OS, DFS). The incidence of LN involvement depends on the histologic type, stage, differentiation and size of the tumor, from 15% in patients with mucosal carcinoma to 69.8% of patients with carcinoma invading the serous layer [6]. Despite theses facts, the extent of

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https://doi.org/10.1016/j.ejso.2018.10.538
0748-7983/

Abbreviations

CIT	Curative-Intent Treatment
CI	Confidence Interval
DFS	Disease-Free Survival
DSS	Disease-Specific Survival
GA	Gastric Adenocarcinoma
HR	Hazard Ratio
OS	Overall Survival

lymphadenectomy in the surgical treatment of gastric cancer is still a topic of controversy among surgeons.

Earlier Western randomized clinical trials (RCT) showed that extended lymphadenectomy (D2) does not impact the overall survival (OS), and was associated with increased morbidity and mortality [7,8]. On the other hands, Eastern RCT demonstrated benefits in OS with acceptable and lower morbidity and mortality rates when compared to Western series [9].

A recent retrospective analyzes of the American National Cancer Database for gastric cancer, including 40,281 patients, showed that the extent of lymphadenectomy is a marker of improved resection, which reflects, in a longer overall survival [10]. The resection of ≥29 nodes was associated with a significantly higher 30-day mortality (4.3%) compared to resection of 15–28 nodes and <15 nodes (3.0% and 2.1%, respectively; $P < 0.001$) [10].

The aim of this study was to analyze the impact on overall survival of oncologic gastrectomy with extended lymphadenectomy, performed in a single cancer center by a specialized foregut group with a standardized technique based on the Eastern experience which prioritizes D2 lymphadenectomy as much as possible.

Methods

Subject and data collection

The data were extracted from a departmental prospective maintained database in the Barretos Cancer Hospital in Brazil, which contains demographic, clinical, operative, pathological and follow-up data. This study was performed within the agreement of institutional board review according to internal policy for protected health information, and patients' permission was obtained by informed consent statement. Postoperative complications were collected retrospectively on medical records and included in the analysis according to the grade of complications by Dindo-Clavien classification [11]. They were evaluated as presence of any complication (grade 1–5 of Dindo-Clavien classification), presence of major complication (grade 3–5), and death (grade 5) at 30-days. The estimated blood loss, and transfusion rates were not fully available and thus they were neither evaluated nor described. All patients included underwent open gastrectomy for gastric adenocarcinoma (GA), performed by the same team of the Barretos Cancer Hospital. The study included patients undergoing curative treatment based on physical examination, performance status, preoperative imaging including endoscopy and computerized tomography of chest, abdomen, and pelvis. Patients were selected to D1 versus D2 group based on age and performance status. All patients with metastatic disease, patients receiving palliative treatment or other forms of resection than gastrectomy were excluded from the

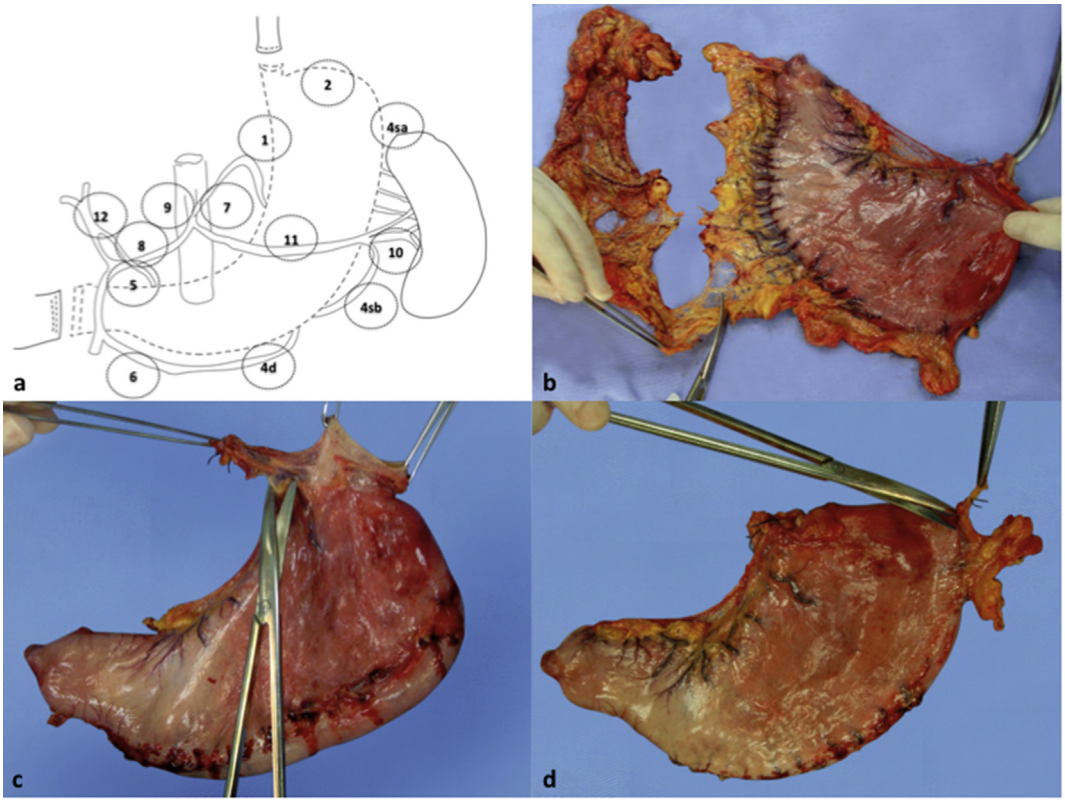

Fig. 1. Standardization of nodal harvesting and specimen preparation. **1a** represents a scheme of nodal harvesting according to nodal stations: 1 - right cardial; 2 - left cardial; 3 - lesser curvature; 4 - greater curvature (4sa, 4sb, and 4d); 5 - suprapyloric; 6 - infrapyloric; 7 - left gastric artery; 8 - common hepatic artery; 9 -celiac axis; 10 - splenic hilus; 11 - splenic artery; 12 – hepatic hilum. **1b** a picture showing the specimen preparation with initial releasing of great omentum. 1c and 1d demonstrate the splitting-up of nodal station 1 and 4sa, respectively.

study. Patients considered suitable for surgery underwent exploratory laparotomy, where the curative intent treatment of the surgery was proven (R0, M0). The pathological stages were based on AJCC, TNM 7th edition [12]. The number and size of lesions and lymph node status were based on pathologic examination. Additional treatment modalities, such as chemo and/or radiation therapy, were also reported. The primary endpoint of this study is OS. The duration of follow-up was the period, in months, between the date of the surgery and date of the last checkpoint recorded in the database, or the date of death of the patient.

Operative techniques

Patients included in the study underwent total gastrectomy with Roux en Y esophagojejunal anastomosis, or partial gastrectomy with Roux en Y, Billroth I or II gastrojejunostomy, or esophagogastrectomy with gastric tube reconstruction. The extent of lymphadenectomy was performed according to the international guidelines [8]. Briefly, D1 lymphadenectomy entailed removal of the stomach (partial or total), and harvesting perigastric nodal stations (1–6) including lesser omentum, and greater omentum most of the time and occasionally the nodal station 7 and/or 9 were also removed (D1 plus). For the proposal of this study, D1 and D1 plus were combined in a single category, D1. D2 lymphadenectomy consisted in the removal of the superior omental bursa from transverse mesocolon, greater and lesser omentum, perigastric nodal stations (1–6), and nodal stations of the left gastric artery (7), common hepatic artery (8a), celiac trunk (9), and proximal splenic artery (11p). The nodal stations of splenic hilum (10) were usually removed en bloc with splenectomy, only for tumors in gastric fundus regarding the proximity of the lesion to the nodal stations and attempting to increase the nodal harvesting. Distal pancreatectomy was performed only in cases of direct invasion of the organ. Nodal stations according to the specimen preparation for both D1 and D2 lymphadenectomy for a total gastrectomy are depicted in Fig. 1a–d.

Statistical analysis

The statistical analyses were performed by Fisher's exact test

Table 1
Clinicopathological data according to the extension of lymphadenectomy for patients who underwent curative-intent treatment of gastric cancer.

Characteristics	Total	D2	D1	p value
Overall	n = 656	536 (81.7)	120 (18.3)	–
Median age	64 (54–71)	63 (54–70	65 (57–74)	0.07
Age				0.004
≥ 70-y	194 (29.6)	145 (27)	49 (40.8)	
< 70-y	462 (70.4)	391 (73)	71 (59.2)	
Gender				0.585
Male	455 (69.4)	369 (68.8)	86 (71.7)	
Female	201 (30.6)	167 (31.2)	34 (283)	
BMI *				0.907
< 25	313 (59.9)	174 (40.4)	36 (39.1)	
≥ 25	210 (45.1)	254 (59.6)	56 (60.9)	
Tumor grade $^{\alpha}$				0.402
I and II	266 (42.4)	214 (41.6)	52 (46)	
III	361 (57.6)	300 (58.4)	61 (54)	
Tumor location				***0.006***
Distal	326 (49.7)	280 (52.2)	46 (38.3)	
Proximal	330 (50.3)	256 (47.8)	74 (61.7)	
Borrmann classification $^{\beta}$				0.096
0 - II	102 (16.8)	89 (18)	13 (11.4)	
III – IV	507 (83.2)	406 (82)	101 (88.6)	
Tumor size **	6.4 (4–9)	6.2 (4–9)	6.9 (5–9)	0.094
Number of positive nodes $^{\mu}$	3 (0–10)	3 (0–9)	5 (1–15)	***0.003***
Number of removed nodes $^{\mu}$	26 (17–37)	28 (18–40)	20 (13–28)	***<0.001***
Procedure				***<0.001***
Total	397 (60.5)	356 (66.4)	41 (34.2)	
Others	259 (39.5)	180 (33.6)	69 (65.8)	
Combined resection				***0.043***
Yes	93 (14.2)	83 (15.5)	10 (8.3)	
No	563 (85.8)	453 (84.5)	110 (91.7)	
Reconstruction				***<0.001***
Y-roux	483 (73.6)	439 (81.9)	44 (36.7)	
Others	173 (26.4)	97 (18.1)	76 (63.3)	
Margin status (R1)				0.061
Yes	24 (3.7)	16 (3)	8 (6.7)	
No	632 (96.3)	520 (97)	112 (93.3)	
Adjuvant treatment $^{\Omega}$				0.83
Yes	411 (64.5)	338 (64.7)	73 (63.5)	
No	226 (35.5)	184 (35.3)	42 (36.5	
Presence of any complications $^{\lambda}$				0.83
Yes	141 (22)	110 (21)	31 (26.3)	
No	501 (78)	414 (79)	87 (73.7)	
Major complications (grade 3–5) $^{\lambda}$				0.296
Yes	60 (9.3)	46 (8.8)	14 (11.9)	
No	582 (90.7)	478 (91.2)	104 (88.1)	
Death within 30-day $^{\lambda}$				0.326
Yes	28 (4.4)	21 (4)	7 (5.9)	
No	614 (95.6)	503 (96)	111 (94.1)	

Data are expressed as median (interquartile range) or n (%); BMI – Body Mass Index; *n = 523; $^{\alpha}$ n = 627; $^{\beta}$ n = 609; ** n = 306, $^{\mu}$ n = 654; $^{\Omega}$ n = 637; $^{\lambda}$n = 642.

and the Wilcoxon rank sum test to examine categorical and continuous variables respectively. Values were expressed as median (interquartile range), or percentage, as appropriate. A univariate analysis looking for survival probabilities (OS) were estimated by the Kaplan–Meier method and compared by the log-rank test. Factors that were significantly associated with outcomes by univariate analysis (inclusion criterion of $p < 0.1$) were entered into a multivariate analysis to adjust for possible confounders. Multivariate analysis was performed by Cox regression model developed to determine factors independently associated with risk of death. A p value of <0.05 was considered significant for univariate and multivariate analyses. A treatment effect matching using Weilbull regression adjustment to time-to-event was made attempting to balance differences in D1 and D2 groups regarding impact in OS. The selected variables were age ≥70-y, nodal stage ≥3, total gastrectomy, combined resection, proximal tumors and use of adjuvant treatment. Based on the sample size, a power calculation was performed to check if the sample were robust enough to detect differences in OS rates. All statistical analyses were conducted by STATA software version 14.0 (StataCorp, College Station, TX).

Results

From 1994 to 2015, 656 consecutive patients who underwent gastrectomy for GA were evaluated. Clinicopathological and operative data according to lymphadenectomy extension are outlined in Table 1. Patients who underwent D2 procedures present more tumors located distal tumors (52.2 versus 38.3%), less positive lymph nodes (median of 3 versus 5 lymph nodes), more extensive lymph node harvesting (median of 28 versus 20 lymph nodes, $p < 0.001$), more total gastrectomies (66.4 versus 34.2%), more combined resections (15.5 versus 8.3%), and more Y-roux reconstructions (81.9 versus 36.7%). No differences were detected regarding presence of any complications, major complications or 30-day deaths between groups. Regarding over period analysis, the patterns of lymphadenectomy changed over years increasing the number of lymph nodes per harvesting for both D1 and D2 lymphadenectomy as depicted in Supplemental File. The pathological distribution between D1 and D2 groups based on pathological stage (AJCC, 7th edition) were detailed in Table 2.

The median OS for all patients were 31 months and 3-, 5-, and 10-y were 47.6, 40, and 27%, respectively, as showed in Fig. 2a. The median follow-up for all patients was 26 months, and for survivors was 65 months. In the univariate analysis for OS, the risk of death was increased in older patients (≥70-y), high-grade tumors, lesions ≥ 5 cm, positive lymph nodes ≥ 3, and extra-gastric resections. Contrary, more extensive lymphadenectomy (D2) improved median OS (37 versus 16 months), 3-y (51.1 versus 32.2%), 5-y (43.2 versus 26), 10-y (30.6 versus 9.4%), as depicted in Fig. 2b. These findings were corroborated in the cox model (HR 0.46, 95% CI 0.33–0.65, $p < 0.001$), as demonstrated in Table 3.

Table 2
Patients distributions according to pathologic stage (AJCC, TNM 7th Edition).

Stage	Overall N = 656 (%)	D2 N = 536 (81.7)	D1 N = 120 (18.3)
0	4 (0.6)	2 (0.4)	2 (1.7)
IA	68 (10.4)	58 (10.8)	10 (8.3)
IB	55 (8.4)	50 (9.3)	5 (4.2)
IIA	18 (2.7)	16 (3)	2 (1.7)
IIB	100 (15.2)	91 (17)	9 (7.5)
IIIA	63 (9.6)	50 (9.3)	13 (10.8)
IIIB	90 (13.7)	76 (14.2)	14 (11.7)
IIIC	165 (25.2)	131 (24.4)	34 (28.3)
IV	93 (14.2)	62 (11.6)	31 (25.8)

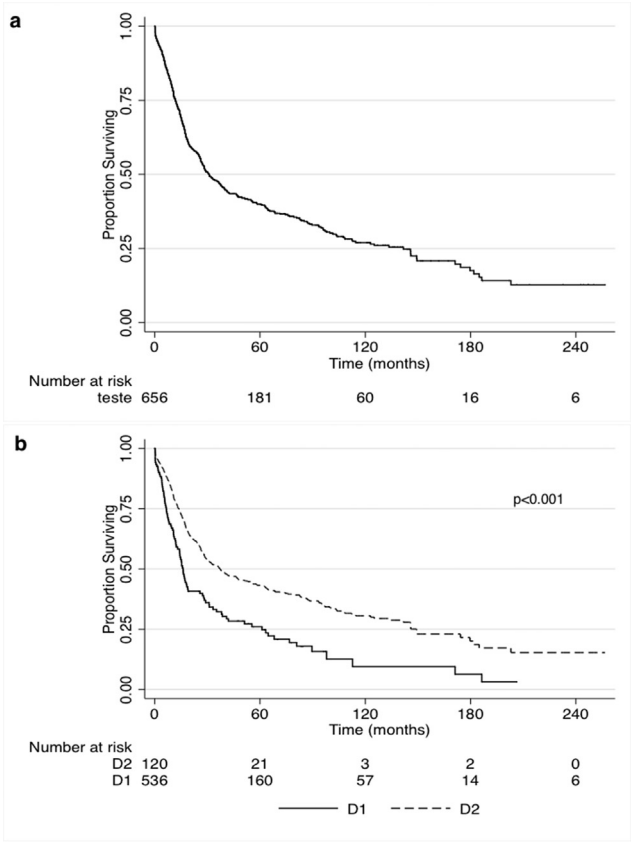

Fig. 2. Kaplan-Meier estimates of Overall survival from the date of gastrectomy, in months, for 656 patients with gastric adenocarcinoma. **2a** represents general overall survival, and **2b** represents overall survival according to the extension of lymphadenectomy (D1 versus D2).

Moreover, the treatment effect matching for time-to event analysis of D2 versus D1, adjusted by the independent variables cited above and 532 observations, showed that D2 lymphadenectomy increased the time to event (death) in 71 months (5.9 years) when compared to D1. Given the sample size of 656 patients, this analysis had an approximately 100% power to detect an HR 0.48 between groups of patients who underwent or not D2 lymphadenectomy, considering p-value of <0.05.

Moreover, nodal status and its relation with OS was also evaluated according to the definition: N0 (none positive node), N1 (until two positive nodes), N2 (from 3 to 6 positive nodes) and N3 (from 7 or more positive nodes) among 654 patients [12]. Regarding the distributions according to nodal status, differences in OS were detected for overall distribution ($p < 0.001$), N0 versus N1, N2 versus N3 ($p < 0.001$), as depicted in Fig. 3a. No differences in OS for N1 versus N2 ($p = 0.41$). However, when nodal status was analyzed adjusted by performing D2 lymphadenectomy or not, the impact of lymphadenectomy increasing OS was evident in patients who presented N1, N2, and N3 nodal status, as demonstrated in Fig. 3b, c, and 3d, respectively. Any significant difference was detected according to the type of lymphadenectomy for patients with N0 nodal stage. Median OS, 3-, 5- and 10-year OS regarding both nodal status and type of lymphadenectomy were demonstrated in Table 4. Briefly, presence of positive node adjusted by extension of lymphadenectomy showed that D2 was also improved median OS for N1 (17.2 versus 7.2 months, $p = 0.018$), N2 (13.3 versus 6.1 months, $p = 0.015$), and N3 (9.1 versus 5.1 months, $p < 0.001$). Moreover, only patients who underwent D2

Table 3
Univariate analysis for overall survival, multivariate analysis for overall survival before and after propensity-score matching.

Characteristics	Total	Overall survival				Univariate analysis	Multivariate analysis ¶		
	N (%)	Median (mo)	3-y	5-y	10-y	p value	HR	95% CI	p value
Overall	656	31	47.6	40	27	–	–	–	–
Age						**0.021**	**1.41**	**1.07–1.87**	**0.016**
<70	433 (66)	31	47.9	40.7	30.2				
≥70	194 (29.6)	30	46.9	38.6	17.8				
Gender						**0.01**	1.22	0.92–1.64	0.173
Male	455 (69.4)	28	44.9	36.6	25.1				
Female	201 (30.6)	51	54	48.1	31.1				
BMI *						**0.005**	0.85	0.65–1.1	0.211
< 25	313 (59.9)	28	45.5	38.8	25.9				
≥ 25	210 (45.1)	64	60.7	51.7	36.6				
Tumor grade α						**0.007**	**1.38**	**1.06–1.82**	**0.017**
I and II	266 (42.4)	47	55.2	48.2	30.5				
III	361 (57.6)	26	41.7	34.6	24.7				
Tumor location						**<0.001**	1.22	0.85–1.48	0.417
Lower	326 (49.7)	41	54.7	45	30.3				
Upper	330 (50.3)	26	40.5	35.1	23.7				
Borrmann classification β						**<0.001**	1.03	0.70–1.52	0.887
0 - II	35 (5.8)	81	70.5	61.8	46.5				
III – IV	67 (11)	29	45.9	38	24.7				
Tumor size **						**<0.001**	1.34	0.99–1.8	0.058
< 5 cm	201 (33.3)	93	71.3	61.4	41.1				
≥ 5 cm	402 (66.7)	24	38.9	33.4	22.4				
Number of positive lymph nodes μ						**<0.001**	**2.38**	**1.77–3.2**	**<0.001**
< 3	310 (47.4)	96	69.2	60.9	43.6				
≥ 3	344 (52.6)	17	28	21.3	12.1				
Procedure						**<0.001**	1.2	0.87–1.66	0.275
Total	397 (60.5)	26	43.1	35.3	24.4				
Others	259 (39.5)	41	54.2	47.1	31				
Combined resection						**<0.001**	**1.63**	**1.14–2.35**	**0.008**
Yes	93 (14.2)	38	51.2	43.5	29.5				
No	563 (85.8)	15	22.3	15.4	9.1				
D2 Lymphadenectomy						**<0.001**	**0.46**	**0.33–0.65**	**<0.001**
Yes	536 (81.7)	37	51.1	43.2	30.6				
No	120 (18.3)	16	32.2	26	9.4				
Reconstruction						0.5	–	–	–
Y-roux	483 (73.6)	–	–	–	–				
Others	173 (26.4)	–	–	–	–				
Margin status (R0)						0.35	–	–	–
Yes	24 (3.7)	–	–	–	–				
No	632 (96.3)	–	–	–	–				
Adjuvant treatment Ω						**<0.001**	**1.42**	**1.02–1.99**	**0.041**
Yes	411 (64.5)	94.8	38.5	30.2	18.8				
No	226 (35.5)	24	67	60.3	44.3				
Presence of major complications λ						**<0.001**	**2.4**	**01.53–3.72**	**<0.001**
Yes	60 (22)	1.8	23.8	19.8	16.8				
No	582 (78)	36.2	50.2	42.7	28.7				

BMI – Body Mass Index; mo – months; *n = 523; α n = 627; β n = 609; ** n = 306, μ n = 654; Ω n = 637; λn = 642; ¶ n = 455; HR – Hazard Ratio; CI – Confidence Interval.

lymphadenectomy achieved 10-year OS, even patients with N2 and N3 nodal stage. Regarding a match comparison for time to event based on a Weilbull regression adjustment using presence of age ≥70-y, nodal stage ≥3, total gastrectomy, combined resection, proximal tumors and use of adjuvant treatment, the D2 lymphadenectomy seemed to increased the mean time to event in 5.9 year later than patients who underwent to D1 lymphadenectomy ($p < 0.001$).

Discussion

The role of lymphadenectomy in gastric cancer remains in debates and represents important differences in worldwide surgical practice. The rationale of local control of gastric cancer spreading seems to be overly radical and unnecessary regarding some Western clinical trials [7,13]. Hartgrink et al. reported 711 patients who underwent gastrectomy for gastric cancer and were randomly assigned to D1 (380 patients) versus D2 (331 patients) with a median follow-up of 11 years [8]. The D2 lymphadenectomy significantly increased morbidity (43% versus 25%) and mortality (10% versus 4%), without significant benefit in OS (35% versus 30%, $p = 0.53$). There was a clear relation between the extensions of lymphadenectomy and the increasing of relative risk ratio of morbidity and mortality, furthermore in an epoch when lymphadenectomy of nodal stations 10 and 11 demanded respectively distal pancreatectomy and splenectomy [8]. Latterly, the INT 0116 showed benefits with adjuvant chemo and radiotherapy compared to surgery alone for patients with gastric and gastroesophageal junction cancer regarding OS with 50% versus 41% in 3 years and median OS 36 versus 27 months, $p = 0.005$ [14]. This approach became the standard in Western countries, however, the strongest criticism about this trial is that only 10% of patients underwent D2 lymphadenectomy, thus it seemed that chemo-radiation represents a putative benefit for patients who underwent incomplete surgical treatment. The MAGIC trial used perioperative chemotherapy versus alone and also demonstrated increasing in OS for gastric, gastroesophageal, and lower esophagus adenocarcinoma [15]. The perioperative group achieved 5-y OS rates 36.3% versus 23% in the

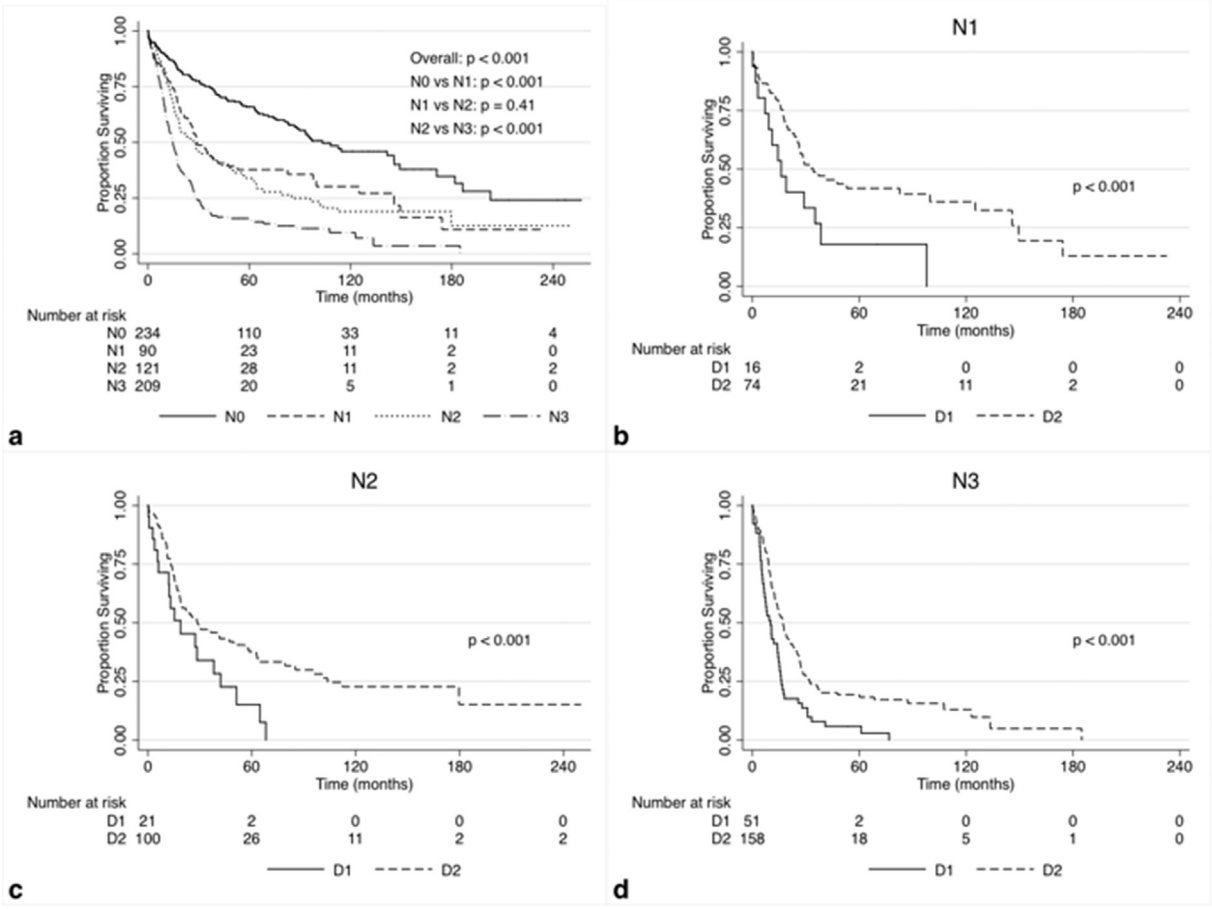

Fig. 3. Kaplan-Meier estimates of overall survival from the date of gastrectomy, in months, for 654 patients with gastric adenocarcinoma according to nodal stage N0 (none positive node), N1 (until two positive nodes), N2 (from 3 to 6 positive nodes) and N3 (from 7 or more positive nodes). **3a** represents general overall survival for nodal status; **3b**, **3c**, and **3d** represent overall survival according to the extension of lymphadenectomy for patients with N1, N2, and N3 respectively.

Table 4
Overall survival according to nodal status and type of lymphadenectomy of 654 patients who underwent gastrectomy for gastric cancer.

Nodal Status	Total	Overall survival				p value
		Median (mo)	3-y	5-y	10-y	
N0	234	103.4	75.1	65.9	45.9	
N0 versus N1						***< 0.001***
N1	90	29.2	44.9	37.8	30.2	
N1 versus N2						0.41
N2	121	27.3	45	33.9	19	
N2 versus N3						***< 0.001***
N3	211	14.8	19.3	15.9	9.5	
According to D2 lymphadenectomy or not						
N0						0.97
D2	202	103.4	74.9	65	46.5	
D1	32	112.8	76.9	72.3	39.6	
N1						***0.018***
D2	74	17.2	48.8	41.8	36.1	
D1	16	7.2	26.8	17.9	–	
N2						***0.015***
D2	100	13.3	47.2	37.7	22.8	
D1	21	6.1	34.1	15.1	–	
N3						***< 0.001***
D2	158	9.1	23.3	19.4	13	
D1	21	5.1	7.8	5.9	–	

surgery alone group, but looking for subanalysis of stomach or gastroesophageal junction locations, no significant differences were found. The same concern about D2 lymphadenectomy was found regarding at least 40% of patients undergoing D2 procedures (40.4% in surgery alone and 42.5% in perioperative group). It is undeniable the value of additional chemotherapy compared to surgery alone either comparing to perioperative or associated with radiotherapy as adjuvant treatment. But what is questionable the lower rates of D2 lymphadenectomy in those trials [14,15].

Otherwise, the Eastern studies have shown an increase in long-term outcomes due D2 lymphadenectomy with acceptable and lower mortality rates. Wu et al. showed in an RCT, benefits in long-term outcomes comparing extended lymphadenectomy (D3) with less extended (D1) lymphadenectomy for gastric cancer [9]. Patients who underwent D3 surgery presented 5-y OS of 59·5% versus 53·6% ($p = 0·041$) and representing HR 0.49 (95% CI 0.32–0.77, $p = 0.002$) after Cox regression. Although no differences in DFS were detected, disease-specific survival (DSS) was also better in D3 group with HR of 0.72 (0.57–0·91), $p = 0.006$. Interestingly even with Western patients, Songun et al. reported the long-term outcomes of the Dutch Trial (median follow-up of 15.2 years) and also showed benefits in DSS for patients who underwent more extensive lymphadenectomy (D2 versus D1) with HR of 0.74 (95% CI 0.59–0.93, $p = 0.01$) [16]. Mocellin et al. showed in systematic review and meta-analysis of RCT that it seems that extended versus limited lymphadenectomy increases DSS with summary HR of 0. HR = 0.81, (95% CI 0.71–0.92, $p = 0.002$), but this data should be carefully analyzed since there was a considerable heterogeneity ($i2 = 40\%$) that could represent a moderate inconsistency [17].

Although there are uncountable differences between Western and Eastern approach regarding lymphadenectomy for gastric cancer, the larger extension of lymphadenectomy per se does not represent an unequivocal association with improvements in OS. Eastern RCT regarding D3 lymphadenectomy (D2 extension with additional removal of para-aortic lymph nodes) did not show increasing in OS when compared to D2 lymphadenectomy [9,18,19].

The strength of our series comes from the fact that it is one of the largest and longest followed Western series with patients undergoing D2 lymphadenectomy, moreover, our sample size was big enough to detect the stated differences in OS. The long follow-up represents substantial information that clearly splits survival curves according to lymphadenectomy extension. Our Western series achieved lymph node harvesting in the D2 lymphadenectomy similarly to Eastern Series and as preconized by Japanese Gastric Cancer Association [5]. This decision was made in the early beginning of our series and the lymph node harvesting has gotten more representative over the years with improved surgical standardization, and also by methodical specimen preparation by the surgical team before the pathological examination. This approach has been used and disseminated in our tertiary care referral center and it was passed on to many generations of surgical oncology fellows of our institution all years long. It could change the number of lymph nodes harvested even for D1 intention, and we do believe that it results from more detailed analysis of nodal stations when compared to *en bloc* specimen analysis. Moreover, the longer follow-up allows realizing that D2 lymphadenectomy impacts not only the usual 5-y OS but it also impacts 10-y OS. No patient with positive node that did not undergo D2 lymphadenectomy achieved 10-year OS, regardless nodal stage. On the other hand, some patients even with N2 or N3 nodal stage achieved 10-year OS corroborating the positive impact of D2 lymphadenectomy for patients with gastric cancer. Moreover, even after matching process, D2 lymphadenectomy still positively impacted OS. All patients who received adjuvant treatment undergone radiation and chemotherapy with 5-fluorouracil plus leucovorin following the INT0116 trial, and it was equally delivered by D1 and D2 groups [14].

Our study limitations are those related to the biases seen in retrospective studies. The decisions of submitting patients to D1 or D2 lymphadenectomy were based on a reasonable judgment by the operating surgeon based on performance status and age, but not on the extension of disease or procedures. Those points justify the presence of older patients in D1 group, which suggests also a tendency of more comorbidity as well. Otherwise, the extension of disease and procedures are larger in the D2 group since there were more total gastrectomies and combined resections in this group, both prognostic factors for complications and overall survival. Detailed data regarding radio and chemotoxicity resulting from both surgery and adjuvant treatment were not fully available to be described and analyzed. However, it is extremely unlikely that adjuvant treatment toxicity would account for any differences between groups since both of them underwent similar rates of chemo and radiotherapy. Since our data comes from a long period, and it began at 1994, no data was promptly available to count to neither perioperative treatment nor biological agents. We do not consider it as a limitation to address the question of this study, and just as consequence of a long-time overview looking back to more than 2 decades of a single cancer center.

Nowadays, we select our patients to a perioperative approach based on presence of cT3 and positive lymph nodes based on preoperative image, and after to exclude carcinomatosis based on staging laparoscopy [20]. The perioperative approach used to be worldwide considered as the standard of care to treat this population of gastric cancer, but recently perioperative FLOT (fluorouracil, leucovorin, oxaliplatin, and docetaxel) became the new standard of care to treat esophagogastric adenocarcinoma [21]. The FLOT regimen improved both OS (median of 50 versus 35 months) and progression-free survival (median of 35 versus 18 months) [20]. Thus, perioperative FLOT has been considered the new standard treatment for esophagogastric cancer [22].

In summary, it seems that there is no consensus about the extension of lymphadenectomy to treat gastric cancer, regarding retrospective data and also RCT. There are many differences between Western and Eastern approaches to gastric cancer, even more concerning lymphadenectomy. The benefits of D2 versus D1 looking for long-term outcomes were not carried out in Western RCT looking for subgroups of both adjuvant chemo-radiation and perioperative chemotherapy for gastric cancer [14,15]. Our study showed that D2 lymphadenectomy for gastric cancer as an independent good predictor of OS, even after 5-y and until 10-y. We do believe that our study suggests that D2 should be offered as the local control for all patients with GA who have a minimal clinical performance for CIT, particularly for patients with positive nodes.

Conflict of interest

No conflict of interest for any authors.

Acknowledgment

The authors wish to thank Professor Bernard D'Allemagne from IRCAD (Research Institute against Cancer of the Digestive System), Strasbourg, France for his assistance in the manuscript preparation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi:10.1016/j.ejso.2018.10.538.

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