

# Implementation and Early Results of Extended Lymph Node Dissection for Gastric Cancer in a Non-Specialized Western Center<sup>S</sup>

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**Abstract: Background:** The optimal degree of lymph node dissection for gastric cancer is still matter of debate. Particularly, there are serious doubts about the reproducibility of extended lymph node dissection in western surgical units, and no studies to date have investigated factors influencing early results (mortality, major morbidity and reoperation rates) during the learning curve.

**Methods:** Univariate and multivariate analysis of 19 variables on a prospective series of 313 consecutive resections for gastric cancer performed by ten different surgeons. Endpoints were mortality, major morbidity and reoperation rates, calculated within 60 days from the operation.

**Results:** Early results were all independently influenced by the presence of comorbidities alone. ASA status III-IV vs I-II determined a higher operative mortality rate (11.9% vs 0.5%; Odds Ratio 12.3; 95% c.i. 1.53 to 98.1; p .018), a higher major morbidity rate (39.7% vs 16.6%; Odds Ratio 2.71; 95% c.i. 1.51 to 4.88; p .0008) and a higher reoperation rate (9.5% vs 2.1%; Odds Ratio 4.81; 95% c.i. 1.51 to 15.3; p .008).

**Conclusions:** Extended lymph node dissection can be safely implemented into the clinical practice of a non-dedicated western institution by providing adequate coaching from more expert surgeons. This implementation protocol led to acceptable rates of operative morbi-mortality, independently influenced only by the comorbidity status.

**Keywords:** Stomach neoplasms, Surgery, lymph node dissection.

## INTRODUCTION

The optimal degree of lymph node dissection for gastric cancer is still matter of debate. Extended lymph node dissection routinely performed in Eastern centers showed overall survival rates exceeding 70% at five years [1] with less than 1% operative mortality rates [2]. Several dedicated or specialized western centers have reproduced these results [3-8]. On the other hand, two large randomized trials in Europe [9, 10], have failed to show any survival advantage and unacceptable morbidity and mortality rates for extended lymph node dissection, mainly due to absence of proper training [11], questioning its widespread adoption in western clinical practice. The purpose of this study is a prospective evaluation of factors influencing early results during implementation of extended lymph node dissection in our surgical unit.

## MATERIALS AND METHODS

From January 1998 to September 2008, 422 consecutive patients were submitted to surgery for gastric adenocarcinoma in our unit. Of these, 69 patients (16.4%)

were not resected (23 staging laparotomy/laparoscopy alone, 46 gastro-jejunal bypass or feeding jejunostomy). The remaining 353 cases (83.6%) were submitted to surgical resection of the tumor.

Forty cases were excluded from this study: 22 cases in which the neoplasm was located in the gastric stump after previous gastric resection; 8 cases in which poor general conditions and emergency (bleeding) or a synchronous malignant neoplasm in other organs prompted a palliative resection with D<sub>0</sub> lymph node dissection; 6 cases submitted to resection of a recurrent tumor and 4 cases submitted to neo-adjuvant chemotherapy. The remaining 313 cases constitute the population of this study. All perioperative data of these patients were prospectively recorded into a database, and outpatient follow-up scheduled every six months during the first three years and yearly thereafter, up to the study censor scheduled at November 30<sup>th</sup>, 2008.

## Setting

All the operations were performed according to a standardized protocol of pre-, intra- and post-operative care in a tertiary care, 700-beds hospital of the Italian National Health System. In 1998, extended lymph node dissection (D<sub>2</sub>) according to the JGCA [12] was introduced into the clinical practice of the unit. Two surgeons (MC, GBG) with previous specific training in extended lymph node dissection obtained through stages in Japanese surgical centers, personally monitored its implementation and diffusion, coaching the other eight surgeons participating in the study.

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### Patient-Related Variables

There were 178 males and 135 females; mean  $\pm$  SD age was  $67.3 \pm 11.6$  years (median 69; range 32-95) and it was categorized according to its median value. Concerning the presence of comorbidities, patients were classified utilizing the American Society of Anesthesiologists system: 187 were ASA class I-II and 126 ASA class III-IV. Body mass index (BMI), expressed as  $\text{Kg/m}^2$ , mean  $\pm$  SD was  $25.4 \pm 3.7$  (median 25.4; range 15.2-37.9); for analytic purposes, it was categorized according to its median value.

### Neoplasm-Related Variables

Location of the tumor was classified according to JGCA rules [12] into lower third, middle third and upper third. Eight cases of diffuse tumors (Borrmann IV type) were classified according to their prevalent location and 15 cardia cancers (Siewert [13] type II) were classified as upper third tumors.

The mean  $\pm$  SD maximum diameter of the tumor was  $47.2 \pm 27.8$  mm (median 40; range 5-160) and it was classified according to its median value. The UICC-TNM staging system, Fifth Edition [14], was used to define depth of invasion (pT), nodal status (pN), distant metastases (pM), stage grouping and grading. Microscopic type was defined according to Lauren [15].

### Treatment-Related Variables

All operations were carried out in an elective setting under a strict perioperative care protocol including antibiotic and antithromboembolic prophylaxis. Access was always through a laparotomic approach, either a midline or a bilateral subcostal incision, depending upon body shape, tumor location and surgeon's preferences. Peritoneal lavage for cytopathologic examination was always obtained in any case with serosal tumor or beyond. A distal subtotal gastrectomy ( $\geq 2/3$ ) was carried out whenever it was possible to obtain a 4 cm macroscopic proximal margin from the edge of the tumor. In closer proximity of this margin and in case of any doubt, a frozen section of the resection margin was obtained and a total gastrectomy eventually performed. In all other cases, a total gastrectomy, eventually extended to lower esophagus through a trans-hiatal approach, was performed. Only in four upper third locations a proximal subtotal gastrectomy was carried out, and in two of these a right thoracotomy was added to control the upwards esophageal spread of the neoplasm. Digestive tract continuity was always restored through a Roux-en-Y manual gastro-jejunal or stapled esophago-jejunal anastomosis.

A standard D<sub>2</sub> (extended) lymph node dissection according to the JGCA [12] was performed in 190 cases. In 27 of these, when the tumor was located in the lower third and was macroscopically infiltrating the serosal layer or beyond (T<sub>3</sub>-T<sub>4</sub>), dissection of lymph nodes posterior to the common hepatic artery and of the hepatic pedicle was added. A more limited lymph node dissection was performed in the remaining 123 cases. A D<sub>1 $\alpha$</sub>  lymph node dissection, namely removal of the first tier of perigastric nodes and of left gastric artery nodes, was performed in 68 patients with higher operative risk (ASA class III-IV); a D<sub>1 $\beta$</sub>  lymph node dissection, namely removal of the first tier of perigastric nodes, of left gastric artery, anterior to the common hepatic

artery and celiac artery nodes, was performed in 55 patients with tumor located in the middle or upper third on the lesser curve and/or on the anterior wall.

Adjacent organs were removed en-bloc only when macroscopically invaded by the tumor. A pancreas-preserving splenectomy [16], was performed with a total gastrectomy in case of upper third locations along the greater curvature and/or on the posterior wall. A prophylactic cholecystectomy was performed in all D<sub>2</sub> resections. At the study censor, seven out of ten participating surgeons performed at least ten cases. One surgeon (GBG, surgeon #1) performed more than 50% of the operations. All the surgical specimens were formalin-fixed, sent en-bloc and processed as usual by ten pathologists who also performed lymph node retrieval without any fat-clearing method. The mean  $\pm$  SD number of examined lymph nodes per patient was  $28.3 \pm 14.1$  (median 26, range 2-78); It was  $17.8 \pm 9.4$  (median 15, range 2-52) after D<sub>1 $\alpha$</sub>  lymph node dissection and  $34.0 \pm 13.9$  (median 32, range 9-78) after D<sub>2</sub> lymph node dissection. Surgical radicality (pR) was defined according to UICC-TNM staging system [14]. Time-trend performance was evaluated including the accrual year as an interval variable.

### Endpoints and Statistical Analysis

Early results (operative mortality, major operative morbidity and reoperation rates) were defined and calculated as any death, major complication or reoperation occurring within 60 days from surgery or during hospitalization when beyond the 60 days limit.

Major complications were defined and recorded as any adverse event requiring any kind of medical intervention and/or prompting any deviation from the perioperative protocol (duration of antibiotic or anticoagulant prophylaxis/therapy, blood transfusions, time to surgical drains removal, interventional radiology, reoperation, length of postoperative hospital stay, etc.), and classified as it follows: Anastomotic dehiscence, as any clinical or radiological evidence of esophago-jejunal or gastro-jejunal anastomotic leakage; Duodenal stump dehiscence, as any clinical or radiologic evidence of duodenal stump leakage; Abdominal haemorrhage, as any postoperative drop of haemoglobin level  $> 25\%$  requiring blood transfusions; Abdominal abscess, as any clinical or radiological evidence of infected peritoneal fluid collection; Pancreatic fistula, as prolonged ( $> 5$  days) drainage of fluid ( $> 50$  mL per day) with at least 3:1 concentration in amylase/lipase levels compared to serum; Major cardiac events, including myocardial ischemia/infarction, worsening of chronic heart failure or acute heart failure, new onset of dysrhythmias; Bronchopulmonar, including any infection, deep venous thrombosis and pulmonary embolism.

All data were analyzed with StatsDirect<sup>®</sup> statistical software, version 2.7.7 (StatsDirect Ltd., UK). Univariate analysis were performed applying Pearson correlation, Chi Square test or Fisher's exact test as appropriate. All significant variables were considered into a multivariate analysis using multiple linear or logistic regression as appropriate, with a non-conditional model [17]. The logistic model's goodness of fit was tested applying the likelihood

ratio test and the Hosmer-Lemeshows test. Statistical significance was assumed for p values < .05.

## RESULTS

At the study censor we recorded 16 deaths within 60 days from the operation (overall operative mortality rate 5.1%), 81 major morbidities (overall major morbidity rate 25.9%) and 16 reoperations (overall reoperation rate 5.1%). Details about these results are described in Table 1.

**Table 1. Details of Early Results**

	Deaths		Morbidities		Reoperations	
	No.	%	No.	%	No.	%
Anastomotic dehiscence	5	1.6	9	2.9	3	0.9
Duodenal stump dehiscence	2	0.6	13	4.1	3	0.9
Abdominal haemorrhage	2	0.6	9	2.9	4	1.3
Abdominal abscess	2	0.6	18	5.9	6	2.0
Pancreatic fistula	--	--	5	1.6	--	--
Major cardiac events	5	1.6	12	3.8	--	--
Bronchopulmonar	--	--	15	4.8	--	--
<b>Total</b>	<b>16</b>	<b>5.1</b>	<b>81</b>	<b>25.9</b>	<b>16</b>	<b>5.1</b>

After univariate analysis (Tables 2-4), Gender, Age, ASA status and Type of lymph node dissection were considered into a multivariate analysis for operative mortality (Table 5); Age, ASA status, pM, Surgeon #1 vs others and pR for operative morbidity (Table 6); ASA status was the only variable independently influencing both mortality and major morbidity rates. Concerning the reoperation rate, at univariate analysis it was significantly influenced only by ASA status (ASA III-IV vs I-II 9.5% vs 2.1%; Odds Ratio 4.81; 95% c.i. 1.51 to 15.3; p .008).

## DISCUSSION

We failed to find any previous report analyzing factors influencing early results of extended lymph node dissection

during the learning curve of ten different surgeons in a western non-dedicated surgical oncology unit. Overall rates of mortality (5.1%), major morbidity (26.9%) and reoperation (5.1%) in this series are well within the range reported in western centers [6-8]. The nearest comparable study is probably the one from the European Oncology Institute [6], in which two experienced surgeons operated 250 consecutive patients from 1994 to 2002, with a lymph node dissection philosophy very close to the one applied in the present series (splenectomy or splenopancreatectomy rate below 10%). Mortality, morbidity and reoperation rates were 1.2%, 18% and 3.6%, respectively. An Italian multicenter prospective trial [7], showed 0.6% mortality and 13.6% morbidity rates, but its exclusion criteria make it unsuitable for extrapolation into clinical practice. Looking at population-based studies, data from about 13,000 cases of the National Inpatient Sample [18], in the USA during the period 1998-2003 showed an operative mortality rate at 6%; this rate was independently influenced by gender (higher in males), by the type of gastric resection (higher for total gastrectomy), by age (higher in older than 50 years) and by hospital caseload (higher in centers performing < 4 cases per year). Similarly as in other western series [6-8], [18-21], early results in our experience were independently influenced only by the presence of significant comorbidities and no other variable.

Particularly, early results were not independently influenced by BMI in our series, in which more than half of the patients were overweight (BMI > 25), confirming similar results in other western series [22,23]. Conversely, overweight significantly influenced morbidity and mortality rates in eastern series [24,25], in which only 10-15% of patients are overweight. This can reflect the fact that western surgeons are more used in operating on more "fatty" patients.

As expected, our analysis does not confirm the unacceptable morbidity (43-46%) and mortality (10-13%) rates in the D<sub>2</sub> arm of Dutch and British randomized trials [9,10]. This is probably due to the voluntary selection bias of patients in the D<sub>2</sub> arm during this implementation study. The concept of standardizing extended lymph node dissection

**Table 2. Early Results According to Patient-Related Variables**

Variable	Pattern	No.	%	Mortality			Morbidity			Reoperation		
				No.	%	p	No.	%	p	No.	%	p
Gender	Males	178	56.9	13	7.3	.043	45	25.3	.781	12	6.7	.213
	Females	135	43.1	3	2.2		36	26.7		4	3.0	
Age	≤ 69 years	151	48.2	1	0.7	< .001	30	19.9	.019	7	4.6	.723
	> 69 years	162	51.8	15	9.3		51	31.5		9	5.5	
ASA status	I-II	187	59.7	1	0.5	< .001	31	16.6	< .001	4	2.1	.008
	III-IV	126	40.3	15	11.9		50	39.7		12	9.5	
BMI (Kg/m <sup>2</sup> )	≤ 25.4	152	48.6	9	5.9	.707	42	26.1	.999	7	4.6	.889
	> 25.4	161	51.4	7	4.3		39	25.6		9	5.6	

ASA: American Society of Anesthesiologists; BMI: Body Mass Index.

**Table 3. Early Results According to Tumor-Related Variables**

Variable	Pattern No.		%	Mortality			Morbidity			Reoperation		
				No.	%	p	No.	%	p	No.	%	p
Location	Lower 3 <sup>rd</sup>	171	54.6	8	4.7	.718	46	26.9	.898	10	5.8	.809
	Middle 3 <sup>rd</sup>	72	23.0	5	6.9		18	25.0		3	4.2	
	Upper 3 <sup>rd</sup>	70	22.4	3	4.3		17	24.3		3	4.3	
Diameter	≤ 40 mm	160	51.1	9	5.6	.869	39	24.4	.622	10	6.2	.497
	> 40 mm	153	48.9	7	4.6		42	27.4		6	3.9	
Depth of invasion	pT <sub>1</sub>	57	18.2	5	8.8	.124	13	22.8	.258	4	7.0	.784
	pT <sub>2</sub>	137	43.8	3	2.2		31	22.8		7	5.1	
	pT <sub>3</sub>	108	34.5	8	8.0		32	29.6		5	4.6	
	pT <sub>4</sub>	11	3.5	0	0.0		5	45.4		0	0.0	
Lymph node status	pN <sub>0</sub>	129	41.2	5	3.9	.781	33	25.6	.252	7	5.4	.940
	pN <sub>1</sub>	74	23.7	5	6.8		15	20.5		3	4.1	
	pN <sub>2</sub>	63	20.1	3	4.6		16	24.6		3	4.6	
	pN <sub>3</sub>	47	15.0	3	6.5		17	36.9		3	6.5	
Distant metastases	pM <sub>0</sub>	286	91.4	14	4.9	.637	67	23.4	.003	15	5.2	.817
	pM <sub>1</sub>	27	8.6	2	7.4		14	51.9		1	3.7	
Stage	I a	52	16.6	5	9.6	.215	13	25.0	.152	4	7.7	.956
	I b	67	21.4	0	0.0		15	22.4		3	4.5	
	II	54	17.3	3	5.5		10	18.5		2	3.7	
	III a	38	12.1	1	2.6		9	23.7		2	5.3	
	III b	33	10.5	2	5.7		8	22.8		2	5.7	
	IV	69	22.1	5	7.5		26	38.8		3	4.5	
Grading	G1	17	5.4	2	11.8	.257	5	29,41	.126	2	11.8	.391
	G2	108	34.5	7	6.5		35	32,41		6	5.5	
	G3-4	188	60.1	7	3.7		41	21,80		8	4.2	
Microscopic type	Intestinal	184	58.8	9	4.9	.832	47	25.5	.871	10	5.4	.756
	Non-intestinal	129	41.2	7	5.4		34	26.3		6	4.6	

while limiting the rate of splenic or splenopancreatic resection in order to increase its implementability in western centers is not new [26, 27], and it was confirmed in our experience (adjacent organs were resected only in 16.6% of cases and a pancreatic resection was carried out only in 3.2% of cases). The main issue remains how to reach this target without jeopardizing the unique opportunity to perform a R<sub>0</sub> resection. The great effort during this implementation study was to spread the main concept of removing the second tier of lymph nodes, or the nodes around the celiac axis and its

branches. This was obtained through a strict perioperative protocol and extensive coaching from more experienced surgeons, leading to a satisfactory homogenization of early results. None of the considered outcomes, actually, was significantly influenced by any of the surgeon-related variables. Only a future study on long-term follow-up on the same series will answer the question if this process of standardization offers an equal homogenization in long-term disease control.

Table 4. Early Results According to Treatment-Related Variables

Variable	Pattern No.		%	Mortality			Morbidity			Reoperation		
				No.	%	p	No.	%	p	No.	%	p
Gastric resection	Subtotal	213	68.1	12	5.6	.540	55	25.8	.973	12	5.6	.540
	Total	100	31.9	4	4.0		26	26.0		4	4.0	
Lymph node dissection	D <sub>1α-β</sub>	123	51.1	12	9.7	.002	37	30.1	.217	7	5.7	.708
	D <sub>2</sub>	190	48.9	4	2.1		44	23.1		9	4.7	
Resection of adjacent organs	None	261	83.4	16	6.1	.339	65	24.9	.091	14	5.3	.076
	Spleen	39	12.5	0	0.0		9	23.1		0	0.0	
	Spleen + pancreas	10	3.2	0	0.0		6	60.0		2	20.0	
	Other	3	0.9	0	0.0		1	33.3		0	0.0	
Surgeon	#1	174	55.6	7	4.0	.471	37	21.3	.039	7	4.0	.471
	Others	139	44.4	9	6.5		44	31.6		9	6.5	
Single surgeon	#1	174	55.6	7	4.0	.344	37	21.3	.069	7	4,02	.169
	#2	34	10.9	3	8.8		13	38.2		3	8,82	
	#3	29	9.3	1	3.4		6	20.7		4	13,79	
	#4	18	5.7	3	16.7		9	50.0		2	11,11	
	#5	13	4.1	1	7.7		2	15.4		0	0,00	
	#6	11	3.5	0	0.0		3	27.3		0	0,00	
	#7	10	3.2	0	0.0		2	20.0		0	0,00	
	Others	24	7.7	1	4.2		9	37.5		0	0,00	
Radicality	pR <sub>0</sub>	261	83.4	12	4.6	.405	58	22.2	< .001	14	5.4	.481
	pR <sub>1</sub>	23	7.3	1	4.3		6	26.1		0	0.0	
	pR <sub>2</sub>	29	9.3	3	10.3		17	58.6		2	6.9	
Accrual year	1998	24	7.7	2	8.3	.386	5	20.8	.234	1	4.2	.717
	1999	23	7.4	1	4.3		4	17.4		1	4.3	
	2000	29	9.3	3	10.3		9	31.0		3	10.3	
	2001	30	9.6	0	0.0		5	16.7		0	0.0	
	2002	31	9.9	1	3.2		13	41.9		3	9.7	
	2003	29	9.3	2	6.9		6	20.7		1	3.4	
	2004	30	9.6	0	0.0		6	20.0		2	6.6	
	2005	37	11.8	3	8.1		8	21.6		2	5.4	
	2006	25	7.9	3	12.0		7	28.0		1	4.0	
	2007	30	9.6	0	0.0		7	23.3		0	0.0	
	2008	25	7.9	1	4.0		11	44.0		2	8.0	

**Table 5. Multiple Variable Analysis for Operative Mortality**

Variable	Pattern	Operative Mortality		Coefficient	Coefficient SE	Odds Ratio	95% c.i.	p
		No.	%					
Gender	Males	13	7.3	-0.90	0.68	0.41	0.10-1.54	.186
	Females	3	2.2					
Age	≤ 69 years	1	0.7	1.68	1.07	5.39	0.66-44.2	.116
	> 69 years	15	9.3					
ASA status	I-II	1	0.5	2.51	1.06	12.3	1.53-98.1	.018
	III-IV	15	11.9					
Lymph node dissection	D <sub>1α-β</sub>	12	9.7	-0.79	0.63	0.45	0.13-1.55	.208
	D <sub>2</sub>	4	2.1					
Intercept				-3.74	1.82			.039

SE: standard error; c.i.: confidence interval; ASA: American Society of Anesthesiologists.  
 Deviance (likelihood ratio) chi-square = 31.569511 df = 4 P < .001.  
 Hosmer-Lemeshow test = 8.38864 df = 5 P = .136.

**Table 6. Multiple Variable Analysis for Operative Morbidity**

Variable	Pattern	Operative Morbidity		Coefficient	Coefficient SE	Odds Ratio	95% c.i.	p
		No.	%					
Age	≤ 69 years	30	19.9	0.19	0.30	1.21	0.67-2.21	.519
	> 69 years	51	31.5					
ASA status	I-II	31	16.6	0.98	0.30	2.66	1.47-4.80	< .001
	III-IV	50	39.7					
pM	pM <sub>0</sub>	67	23.4	-0.68	1.15	0.50	0.05-4.87	.554
	pM <sub>1</sub>	14	51.9					
Surgeon	#1	37	21.3	0.45	0.28	1.58	0.91-2.76	.106
	Others	44	31.6					
pR	pR <sub>0</sub>	58	22.2	-0.34	0.52	0.71	0.25-1.98	.514
	pR <sub>1</sub>	6	26.1					
	pR <sub>2</sub>	17	58.6					
Intercept				-2.15	0.63			< .001

SE: standard error; c.i.: confidence interval; ASA: American Society of Anesthesiologists.  
 Deviance (likelihood ratio) chi-square = 35.666393 df = 5 P < .001.  
 Hosmer-Lemeshow test = 8.109729 df = 5 P = .15.

In conclusion, extended lymph node dissection can be safely implemented into the clinical practice of a non-dedicated western institution by limiting the rate of splenopancreatectomy and providing adequate coaching from more expert surgeons.

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**CONFLICT OF INTEREST**

The authors declare that they have no conflict of interest.

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