

# World Journal of *Gastroenterology*

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## Retrospective Cohort Study

# Postoperative mortality and morbidity after D2 lymphadenectomy for gastric cancer: A retrospective cohort study

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## Abstract

### BACKGROUND

Surgery for gastric cancer is a complex procedure and lymphadenectomy is often mandatory. Postoperative mortality and morbidity after curative gastric cancer surgery is not insignificant.

### AIM

To evaluate the factors determining mortality and morbidity in a population of patients undergoing R0 resection and D2 lymphadenectomy for gastric cancer.

### METHODS

A retrospective analysis of clinical data and pathological characteristics (age, sex, primary site of the tumor, Lauren histotype, number of positive lymph nodes resected, number of negative lymph nodes resected, and depth of invasion as

data used are present in the text. No additional data are available.

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defined by the standard nomenclature) was conducted in patients with gastric cancer. For each patient we calculated the Kattan's score. We arbitrarily divided the study population of patients into two groups based on the nomogram score ( $< 100$  points or  $\geq 100$  points). Prespecified subgroups in these analyses were defined according to age ( $\leq 65$  years or  $> 65$  years), and number of lymph nodes retrieved ( $\leq 35$  lymph nodes or  $> 35$  lymph nodes). Uni- and multivariate analysis of clinical and pathological findings were performed to identify the factors affecting postoperative mortality and morbidity.

## RESULTS

One-hundred and eighty-six patients underwent a curative R0 resection with D2 lymphadenectomy. Perioperative mortality rate was 3.8% (7 patients); a higher mortality rate was observed in patients aged  $> 65$  years ( $P = 0.002$ ) and in N+ patients ( $P = 0.04$ ). Following univariate analysis, mortality was related to a Kattan's score  $\geq 100$  points ( $P = 0.04$ ) and the presence of advanced gastric cancer ( $P = 0.03$ ). Morbidity rate was 21.0% (40 patients). Surgical complications were observed in 17 patients (9.1%). A higher incidence of morbidity was observed in patients where more than 35 lymph nodes were harvested ( $P = 0.0005$ ).

## CONCLUSION

Mortality and morbidity rate are higher in N+ and advanced gastric cancer patients. The removal of more than 35 lymph nodes does not lead to an increase in mortality.

**Key Words:** Gastric cancer; Total gastrectomy; Subtotal gastrectomy; Lymphadenectomy; Kattan's nomogram; Mortality; Postoperative complications; Postoperative pancreatic fistula; Hemoperitoneum; Anastomotic leakage

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**Core Tip:** Surgery for gastric cancer is a complex procedure. The aim of our study is to evaluate the factors determining mortality and morbidity in 186 patients undergoing R0 resection and D2 lymphadenectomy for gastric cancer. Perioperative mortality rate was 3.8%; a higher mortality rate was observed in patients aged  $> 65$  years and in N+ patients. Mortality was related to a Kattan's score  $\geq 100$  points and the presence of advanced gastric cancer. Morbidity rate was 21.0%. Surgical complications were observed in 17 patients. A higher incidence of morbidity was observed in patients where more than 35 lymph nodes were harvested.

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## INTRODUCTION

Although the incidence of gastric cancer is steadily declining, the disease remains the second leading cause of cancer death[1,2]. Currently, surgery is the only potentially curative treatment for gastric cancer[3,4]. The depth of primary tumor invasion, lymph node involvement, and distant metastasis are the major predictors of prognosis for patients with gastric cancer[5].

Node metastases occur during the early stages of the disease, and lymphadenectomy is recommended as the main intervention of a radical surgical treatment[4,6,7]. According to the TNM staging system proposed by the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC)[8], the N stage is classified into 5 Levels based on the number of metastatic lymph nodes. However, the extent of lymphadenectomy, which aims to achieve the highest optimal outcome, has been a controversial topic for a long time with no worldwide consensus





as of yet[9]. A minimum of 16 lymph nodes has been recommended as an adequate number in radical gastrectomy for gastric cancer to ensure reliable N staging. Studies have shown that the number of dissected metastatic lymph nodes influences prognosis [10].

Gastric cancer surgery is a complex procedure; in this context, lymphadenectomy is mandatory[11-14]. Mortality and morbidity after curative gastric cancer surgery are not negligible[15-17]. There are many clinical and pathological factors that induce an increase in mortality and morbidity[18]. The extent of the lymphadenectomy is one of these factors. The development of postoperative complications, and the associated mortality, is also influenced by the stage of the disease, the number of lymph node metastases, the removal of contiguous organs and the age of the patient.

In this paper, we evaluated patients with histologically confirmed gastric adenocarcinoma, who underwent curative gastrectomy and D2 lymphadenectomy according to the Japanese Gastric Cancer Association (JGCA) guidelines[19,20]. The primary endpoint of the study is to evaluate the factors determining mortality and morbidity in a population of patients undergoing R0 resection and D2 lymphadenectomy for gastric cancer. For each patient we calculated the Kattan's score. In agreement with the original report by Kattan *et al*[21] the following prognostic variables were assembled for use in validating the nomogram: age, sex, primary site [distal one-third, middle one-third, proximal one-third, and gastroesophageal junction (GEJ)], Lauren histotype (diffuse, intestinal, mixed), number of positive lymph nodes resected, number of negative lymph nodes resected and depth of invasion as defined by the standard nomenclature. We arbitrarily divided the study population of patients into two groups based on the nomogram score (< 100 points or  $\geq$  100 points). Prespecified subgroups in these analyses were defined according to age ( $\leq$  65 years or > 65 years) and number of lymph nodes retrieved ( $\leq$  35 lymph nodes or > 35 lymph nodes). The cut off was used in this study since age > 65 years is considered a significant risk factor for postoperative complications in gastric surgery, and was also in accordance with a definition of age limits for elderly patients. Clinical factors and pathological findings were evaluated to identify the factors that induce increased postoperative mortality and morbidity in patients undergoing R0 surgery. Treatment factors were also analyzed for their impact on mortality and morbidity.

## MATERIALS AND METHODS

This is a retrospective study. An analysis of clinical data and pathological characteristics was conducted on patients with gastric cancer observed and treated at the General Surgery Operative Unit, Fondazione Policlinico Universitario "A Gemelli" IRCCS, from January 2010 to December 2015, and at the General Surgery Operative Unit, San Giovanni di Dio Hospital, Azienda Sanitaria Provinciale Crotone, from January 2016 to June 2020.

All patients provided written consent before the surgical procedures. Preliminary approval to use patient data was obtained from the Institutional Review Board. This study was conducted according to the STROBE guidelines[22].

### Inclusion criteria

Patients with histologically documented gastric cancer were included in the study. All patients underwent a complete clinical evaluation, including laboratory tests, with complete blood cell count and serum chemistry. In all patients, a preoperative staging of the neoplasm was performed. This included upper digestive endoscopy with biopsy, chest X-ray, liver ultrasound and abdomino-pelvic CT-scan. Tumors were staged according to the latest version of the pathologic classification (pTNM) of the International UICC. The histological classification followed the Lauren criteria[23].

### Exclusion criteria

Gastric stump and linitis plastica type tumors were excluded from the analysis. Patients with squamous cell cancer or stromal tumors and patients in preoperative neoadjuvant treatment protocols were also excluded from the analysis. Patients with positive surgical resection margins, patients with peritoneal carcinomatosis and/or patients with metastatic disease, and patients with > 1 missing data were not included in the study.

### Surgical rules

Gastrectomy is defined by the removal of the greater and lesser omentum and

perigastric lymph nodes (N1 level, station numbers 1-6). Lymphadenectomy is classified as D2 according to the guidelines of the Japanese Gastric Cancer Association [24]. D2 lymphadenectomy involves the en-bloc removal of lymph node stations 7, 8a and 8p, 9, and 11p and 11d. The left gastric artery was suture ligated at its origin. Lymphadenectomy of the splenic hilum (station 10) was always performed. Hepatoduodenal ligament nodes (station numbers 12a, 12b, 12p) were also dissected. Cholecystectomy was performed in all patients. The resection was extended to the distal esophagus when required by tumor spread and location, which was the case in nearly all of the tumors located at the GEJ. Each lymph node station was removed and classified either during the operation or from the surgical specimen; single lymph nodes were retrieved in the fresh specimen and then submitted to histopathological examination.

For reconstruction, the Roux-en-Y technique was performed in all cases. After total gastrectomy, esophagojejunostomy, using an EEA stapler (diameter 25 mm) was used routinely. In case of a subtotal gastrectomy, Roux-en-Y gastrojejunostomy was performed using an EEA stapler (diameter 25 mm) or a linear stapler (60 mm), at surgeon's discretion. A trans-anastomotic tube was placed in all patients.

### **Pathological data**

The surgical specimens and lymph nodes were assessed by pathologists and were classified according to the 8<sup>th</sup> Edition of the UICC/AJCC TNM staging system[8]. The T category was used to assess the depth of invasion. For nodal staging, involvement of lymph nodes was defined as follows: N0, no regional lymph nodes metastasis; N1, metastasis in 1 to 2 regional nodes; N2, metastasis in 3 to 6 regional lymph nodes; N3a, metastasis in 7 to 15 regional lymph nodes; N3b, metastasis in > 16 regional lymph nodes. Based on definitive pathological findings, the potentially curative procedures were classified as radical (R0 - microscopic tumor free) or as R1 (microscopic residual disease) according to the absence or presence of residual tumor. Palliative resection was classified based on R2 (macroscopic disease left behind)[24]. Frozen sections were not routinely used in the evaluation of margins, but only in the suspicion of a possible tumor infiltration.

### **Postoperative course**

Antibiotic prophylaxis was used in all patients. Low molecular weight heparin treatment was used in all patients for 30 d. All patients were mobilized on the first postoperative day. The bladder catheter was removed on the first postoperative day except in clinical emergencies. The ERAS protocol was not used in any patient. The anastomosis was routinely checked prior to the patient resuming oral intake with a radiological examination using water-soluble contrast on postoperative day 4-7. The trans-anastomotic tube was removed after performing the radiological control if no sign of anastomotic leak was observed. The patients were monitored for 30 d postoperatively for complications and mortality. Complications were considered when occurring within 30 d from surgery, and with a Clavien-Dindo severity grade 2 or more[25]. Anastomotic leakage was defined as a full thickness gastrointestinal defect involving esophagus, anastomosis, staple line, gastric or jejunal stump irrespective of presentation or method of identification; an abscess close to the anastomoses is also considered as anastomotic leakage.

The patients follow up was standardized as follows: clinical examination, full blood tests and dosage of tumor markers, chest X-ray and abdominal ultrasound every 3 mo for the first 2 years and every 6 mo for the following 3 years. Digestive endoscopy and total-body CT scan were performed annually, unless otherwise required. The evaluation of the nutritional status was managed by specialized nutritionists. No patients were lost to follow-up procedure. All patients with positive lymph nodes were treated with systemic adjuvant chemotherapy.

### **Statistical analysis**

The clinicopathological characteristics included the patient age, sex, resection type, associated splenectomy, tumor site, histological type, T category, N stage, number of lymph nodes examined, number of metastatic lymph nodes, stage of disease, depth of the primitive tumor and Kattan score. Data are expressed as a mean  $\pm$  SD. Data were analyzed with standard statistical methods using GraphPad Prism Software (GraphPad, CA, United States). Comparison of means  $\pm$  SD was performed with the two tailed *t*-test. A univariate analysis with all the demographic data and pathologic factors using the Fisher's exact test for categorical data and the ANOVA test for continuous data was performed. Subsequently, a multivariate logistic regression was

performed. Regardless of the used test, a *P* value < 0.05 was considered statistically significant.

## RESULTS

During the study period, a total of 304 patients with gastric cancer were treated at the General Surgery Operative Unit, Fondazione Policlinico Universitario “A Gemelli” IRCCS of Rome, and at the General Surgery Operative Unit, San Giovanni di Dio Hospital, Azienda Sanitaria Provinciale of Crotone. Among them, 186 patients (61.2%) underwent a macroscopic potentially curative D2 lymphadenectomy (R0 resection) and were retrospectively analyzed for this observational study. The other 118 patients were excluded from the evaluation for the presence of distant metastases (50 cases, 16.4%), peritoneal carcinosis (44 cases, 14.4%) diagnosed preoperatively either by laparoscopy (31 cases) or by exploratory laparotomy, or due to R2 surgery (24 cases, 7.9%).

### Demographics and intraoperative data

The main demographic data and clinical characteristics of all patients are reported in Table 1. One hundred and eight patients were male (58.1%) and 78 females (41.9%). The mean age was  $64.9 \pm 12.4$  years (range: 24-90 years). One hundred and six patients were older than 65 years (57.0%) and 80 less than or equal to 65 years (43.0%). The mean tumor size was  $4.4 \pm 2.3$  cm (range 0.5-14 cm). With regards to tumor localization a higher percentage of tumors were in the middle or lower third (31.2% and 43.5%, respectively) of the stomach. As far as UICC/AJCC stage groupings, 95 patients (51.0%) were in early stage of the disease (stage IA, IB, IIA) and 91 patients (49.0%) had advanced disease (stage IIB, IIIA, IIIB, IIIC). Only 40 patients (T1a 36 cases - 19.3%, T1b 4 cases - 2.1%) had early gastric cancer (Table 1). Kattan score was  $117.8 \pm 45.7$  points (range 11-215).

Total gastrectomy was performed in 88 patients (47.3%) and subtotal gastrectomy in 98 (52.7%). Mean age of patients undergoing total gastrectomy was  $63 \pm 12.1$  years and  $66.6 \pm 12.5$  years in those undergoing subtotal gastrectomy (*P* = 0.04). In the total gastrectomy patient's subgroup, the mean Kattan score was  $111.3 \pm 44.1$  points, statistically lower (*P* = 0.03) than that observed after subtotal gastrectomy ( $125.1 \pm 46.7$  points). The mean tumor size was  $4.6 \pm 2.6$  cm (range 1-14) and  $4.1 \pm 2.0$  cm (range 0.5-11) in patients undergoing total gastrectomy and subtotal gastrectomy, respectively (*P* = 0.1).

To obtain an R0 resection, adjacent organs were removed in 5 patients (2.7%): in two cases an atypical liver resection was performed, and in 3 a transverse colon resection was performed. A mean number of  $38.3 \pm 10.9$  lymph nodes (range 17-98) were dissected. The average number of positive lymph nodes was  $4.2 \pm 6.3$  (range 0-39). 74 patients were N0. The mean number of lymph nodes removed was  $40 \pm 10.4$  (range 25-93) and  $36.7 \pm 11.1$  (range 17-98) in total gastrectomy and subtotal gastrectomy, respectively (*P* = 0.03). The number of positive lymph nodes was  $4.9 \pm 6.9$  (range 0-39) in patients undergoing total gastrectomy and  $3.5 \pm 5.7$  (range 0-31) in patients undergoing subtotal gastrectomy (*P* = 0.1). Lymphadenectomy of the splenic hilum involved splenectomy in 105 cases (56.4%) and was performed with the spleen-preserving technique in the remaining 81 cases (43.6%). 103 patients (55.3%) had > 35 lymph nodes retrieved. Mean duration of surgical procedures was  $260 \pm 76.1$  minutes. Mean length of postoperative hospital stay was  $12.7 \pm 8.2$  d.

### Mortality

Perioperative mortality rate was 3.8% (7 patients). Causes of death were pancreatic fistula (2 cases), hemoperitoneum (2 cases, one of which was associated with a pancreatic fistula), dehiscence of the esophago-jejunal anastomosis (1 case), dehiscence of the duodenal stump (2 cases) and aspiration pneumonia resulting in ARDS (1 case). A higher mortality was observed in the group of patients aged > 65 years (7 cases out of 80, 8.7%) compared to those aged < 65 years (no cases in 106 patients, *P* = 0.002) and in N+ patients (7 cases out of 112, 6.2%) compared to N- patients (no cases out of 74 patients, *P* = 0.04, Table 2).

In the univariate analysis a significant mortality rate was observed in the group of patients aged > 65 years (*P* = 0.008), in patients with Kattan score  $\geq 100$  points (*P* = 0.04), and in patients with advanced gastric cancer (*P* = 0.03). Sex (*P* = 0.4), type of surgery performed (*P* = 0.8), primary tumor location (*P* = 0.8), tumor depth (*P* = 0.1), and Lauren histological type (*P* = 0.4) had no statistically significant influence on



**Table 1 Clinico-pathologic patient characteristics**

Characteristics		
Sex		
Male	108	58.1%
Female	78	41.9%
Age, yr	64.9 ± 12.4	Range 24-90
Primary tumor location		
Gastroesophageal junction	22	11.8%
Upper third	25	13.4%
Middle third	58	31.2%
Lower third	81	43.5%
Histological type (Lauren classification)		
Enteric type	96	51.6%
Diffuse type	64	34.4%
Mixed type	26	14.0%
Type of resection		
Total gastrectomy	88	
Subtotal gastrectomy	98	
Size, cm	4.4 ± 2.3	Range 0.5-14
Number of lymph nodes retrieved	38.3 ± 10.9	Range 17-98
Number of positive lymph nodes	4.1 ± 3.6	Range 0-39
Operation time, minutes	260 ± 76.1	
Length of stay, d	12.7 ± 8.2	
T status		
T1a	36	19.3%
T1b	4	2.1%
T2	79	42.5%
T3	56	30.1%
T4a	2	1.1%
T4b	9	4.8%
Depth		
Mucosa	14	7.5%
Submucosa	31	16.7%
Muscularis propria	37	19.9%
Subserosa (suspected invasion)	46	24.7%
Subserosa (certain invasion)	49	26.3%
Serosa	4	2.1%
Adjacent structures	5	2.7%
N status		
N0	74	39.8%
N1	37	19.9%
N2	31	16.7%
N3a	33	17.7%

N3b	11	5.9%
Stage AJCC/TNM		
IA	29	15.6%
IB	32	17.2%
IIA	34	18.3%
IIB	35	18.8%
IIIA	23	12.4%
IIIB	26	14.0%
IIIC	7	3.8%

Values are mean  $\pm$  SD. All the patients were included in all evaluations.

perioperative mortality (Table 3). In the multivariate analysis (Table 3) only age > 65 years had a statistically significant influence (T ratio 2.960,  $P = 0.004$ ) on perioperative mortality.

### Postoperative overall complications

Postoperative complications were documented in 40 patients (21.5%). Table 4 Lists the type of complications and their frequency. As shown, pulmonary complications, urinary tract infections, pancreatic fistulas, anastomotic leaks and duodenal fistula were the most frequently observed complications.

A higher incidence of complications was observed in patients undergoing subtotal gastrectomy (29 cases out of 98 patients, 29.5%) compared to those undergoing total gastrectomy (11 cases out of 88 patients, 12.5% -  $P = 0.006$ ), in patients with Kattan score  $\geq 100$  points (32 cases out of 121 patients, 26.4%) compared to those with Kattan score < 100 points (8 out of 65 patients, 12.3% -  $P = 0.02$ ) and in those N + (30 out of 112 patients, 26.7%) compared to those N- (10 of 74 patients, 13.5% -  $P = 0.04$ , Table 2).

Univariate analysis (Table 5) confirmed that sex, age, number of lymph nodes harvested, primary tumor site and histological type are not related to morbidity. This is related to the type of surgery ( $P = 0.005$ ), the Kattan score ( $P = 0.02$ ), the tumor depth ( $P = 0.01$ ), T stage ( $P = 0.006$ ) and the stage of the disease ( $P = 0.01$ ). In the multivariate analysis (Table 5) only the extent of surgery showed a statistically significant correlation (T ratio 2.526,  $P = 0.01$ ).

### Postoperative surgical complications

Surgical complications were observed in 17 patients (9.1%). Among these, the most frequent were duodenal fistula (5 cases), pancreatic fistula (4 cases, one of which associated with hemoperitoneum) and dehiscence of the esophago-jejunal anastomosis. Four patients (2 cases of hemoperitoneum, 2 cases of duodenal fistula) underwent further surgical treatment. The two patients with bowel obstruction underwent adhesion lysis surgery 2 mo and 6 mo after gastric surgery, respectively. All other patients with surgical complications were treated conservatively. A higher incidence of surgical complications was observed in the patient group with more than 35 lymph nodes harvested (16 cases out of 103 patients, 15.5%) compared to patients in which fewer lymph nodes were removed (1 case in 83 patients, 1.2% -  $P = 0.0005$ ). Sex ( $P = 0.7$ ), age > 65 years ( $P = 0.2$ ), type of surgery performed ( $P = 0.6$ ), Kattan score ( $P = 0.1$ ), lymph node positivity ( $P = 0.1$ ) and early stage of disease ( $P = 0.5$ ) did not affect the rate of perioperative surgical complications (Table 2).

This was confirmed by the univariate analysis, which documented that the removal of more than 35 lymph nodes ( $P = 0.002$ ), the depth of the tumor ( $P = 0.04$ ) and the stage of disease ( $P = 0.01$ ) are statistically correlated with the development of surgical complications in the postoperative period (Table 6).

On multivariate analysis (Table 6) only one lymphadenectomy with removal of more than 35 lymph nodes correlates significantly with the rate of surgical complications (T ratio 3.222,  $P = 0.001$ ).

**Table 2 Mortality, overall morbidity and surgical morbidity in all patients**

Characteristics	Number of cases	Mortality	Overall morbidity	Surgical morbidity
	186	7	40	17
Sex				
Male	108	3	24	9
Female	78	4	16	8
		$P = 0.4$	$P = 0.8$	$P = 0.7$
Age				
> 65 yr	80	7	22	10
≤ 65 yr	106	0	18	7
		$P = 0.002$	$P = 0.1$	$P = 0.2$
Type of surgery				
TG	88	3	11	7
STG	98	4	29	10
		$P = 1.0$	$P = 0.006$	$P = 0.6$
Kattan score				
≥ 100 points	121	7	32	14
< 100 points	65	0	8	3
		$P = 0.09$	$P = 0.02$	$P = 0.1$
Lymphadenectomy				
> 35 lymph nodes	103	3	24	16
≤ 35 lymph nodes	83	4	16	1
		$P = 0.7$	$P = 0.5$	$P = 0.0005$
Lymph nodes				
Negative	74	0	10	4
Positive	112	7	30	13
		$P = 0.04$	$P = 0.04$	$P = 0.1$
T				
Early cancer	40	0	5	2
Advanced cancer	146	7	35	15
		$P = 0.3$	$P = 0.1$	$P = 0.5$
Splenectomy	105	4	24	9
Spleen-preserving	81	3	16	8
		$P = 1.0$	$P = 0.7$	$P = 0.8$

TG: Total gastrectomy; STG: Subtotal gastrectomy. All the patients were included in all evaluations. Fisher exact test two-tailed.

## DISCUSSION

Surgical treatment is still the mainstay of curative gastric cancer treatment[4,26-29]. For patients who undergo surgery, prognosis is determined by a series of factors, among which depth of invasion, nodal status, and metastasis are the most important. These factors are part of the UICC/AJCC stage formula, which is the most reliable prognostic system. In addition, certain multivariate analyses could identify extent of lymphadenectomy, lymph node ratio (ratio between positive and removed nodes), residual tumors, and grading, as independent prognostic factors. The expected prognosis has great impact on the kind of treatment a patient will receive. The

**Table 3 Univariate and multivariate analysis of variables associated with postoperative mortality**

	Univariate analysis		Multivariate analysis		
	Number of cases	%	P value	T ratio	P value
Sex (Male)	3	42.9	0.406	0.5888	0.557
Age > 65 yr	7	100	0.008	2.960	0.004
Type of surgery (subtotal gastrectomy)	4	57.1	0.810		
Kattan score $\geq 100$	7	100	0.048	0.9504	0.343
Lymph nodes > 35	6	85.7	0.152	1.745	0.114
Primary site			0.821		
Gastroesophageal junction	1	14.3			
Upper third	1	14.3			
Middle third	1	14.3			
Lower third	4	57.1			
Depth			0.137	1.231	0.220
Mucosa	0				
Submucosa	1	14.3			
Muscularis Propria	0				
Subserosa (suspected invasion)	2	28.6			
Subserosa (certain invasion)	3	42.9			
Serosa	0				
Adjacent structures	1	14.3			
Histological type (Lauren classification)			0.436		
Enteric type	3	42.9			
Diffuse type	2	28.6			
Mixed type	2	28.6			
T status			0.031	1.342	0.181
T1a	0				
T1b	0				
T2	3	42.9			
T3	2	28.6			
T4a	0				
T4b	2	28.6			
Stage AJCC/TNM			0.039	0.6371	0.525
IA	0				
IB	0				
IIA	1	14.3			
IIB	2	28.6			
IIIA	1	14.3			
IIIB	3	42.9			
IIIC	0				

standard for nodal staging of gastric cancer has international variation, and recently significant changes have been made to the AJCC/UICC staging system to simplify lymph node staging in the countries using TNM staging. In the most recent AJCC edition N1 represents 1-6 positive lymph nodes; N2 represents 7-15 positive lymph

**Table 4 Major postoperative complications with a severity grade 2 or more according Clavien-Dindo classification**

Type of complication	Number of cases	%
Pulmonary	12	6.4
Urinary tract infection	10	5.4
Leak of esophago-jejunal anastomosis	4	2.1
Intra-abdominal abscess	1	0.5
Abdominal bleeding	2	1.0
Duodenal fistula	5	2.7
Intestinal occlusion	2	1.0
Pancreatic fistula	4	2.1

nodes; and N3 represents > 15 positive lymph nodes. The cut-off points were determined from retrospective databases[30] and in subsequent evaluations showed a superior predictive ability compared to other staging systems[31,32].

The extent of lymphadenectomy is the only factor that can be influenced by the surgeon[33-38]. The total number of lymph nodes resected, or the total number of positive to negative ratio of lymph nodes have all been found to be predictors of survival in gastric cancer patients[37]. For potentially resectable gastric cancer, a linear trend toward superior survival was found for higher lymph node removal up to 35-40 lymph nodes, based on the analysis of the SEER database from 1973 to 1999[38]. Adjuvant therapy is used in advanced gastric cancer to improve the survival and may be useful in high-risk patients treated with limited lymph node dissection. Moreover, lymph node dissection remains crucial to make every effort to improve the prognosis in those patients unsuitable for any adjuvant treatment[39,40]. In a study Biffi *et al*[13] showed that extended lymph node resection offers survival benefit even in the subgroup of patients with early-stage disease. Evaluation of distant disease-free survival risk by number of harvested lymph nodes showed that the risk of recurrence is inversely proportional to the number of dissected lymph nodes. The results did not change when pT1 and pT2-3 cancers were analyzed separately, suggesting the need to remove at least 15 nodes even in patients with early-stage disease[13].

The idea of an extended lymphadenectomy for gastric cancer was first advanced by Mikulicz in 1889, who stated that the distal pancreas should be removed if necessary [40-42]. Recent studies show that D2 lymphadenectomy improves the accuracy of locoregional staging and might reduce disease recurrence in patients with gastric adenocarcinoma[27]. Furthermore, when expert surgeons perform D2 lymphadenectomy and avoid routine distal pancreatectomy and splenectomy, perioperative morbidity and mortality can be kept to a minimum[43,44].

Although neither the 5-year[28] nor 11-year results[40] of the Dutch trial showed a significant improvement in overall survival for patients randomized to D2 lymphadenectomy compared with D1, we believe that surgery remains the only non-standardized therapy in the context of clinical trials and that D2 resection has clinical relevance in most treatment algorithms. Several surgeons agree that standardized D2 lymphadenectomy is an appropriate and potentially beneficial treatment approach[45, 46]; like any therapy, surgery must be done safely and correctly by skilled clinicians and should be tailored to the patient and biology of the disease[4,47,48].

Marubini *et al*[10] examined 615 resections, and found no difference in mortality (1.8%) or complication rates (12.8%) with respect to the number of harvested nodes, but better overall survival when more lymph nodes were assessed. With more than 11 years of median follow-up, there was a trend for improved survival for patients with N2 disease who had received a D2 dissection[40]. Another analysis excluding patients with distal pancreatectomy and splenectomy found a survival benefit for the D2 resection patients[49]. Clinical series from Asia have found a low rate of nodal recurrences following aggressive lymph nodes dissection. Furthermore, Japanese investigators have recently completed trials of D2 *vs* D2 plus para-aortic nodal dissection, showing better results in small cancer with negative nodes who underwent aggressive D2 dissection[4]. Moreover, if D2 lymphadenectomy was performed, it was likely to have a marked benefit compared to D1 dissection[14,50].

Despite the therapeutic value of lymphadenectomy, mortality and complications are still high in gastric cancer surgery[16,51]. Several studies point out that stomach cancer



**Table 5 Clinicopathological factors associated with overall morbidity by univariate and multivariate analysis**

	Univariate analysis		Multivariate analysis		
	Number of cases	%	P value	T ratio	P value
Sex (Male)	24	60	0.779	0.8443	0.4
Age > 65 yr	22	55	0.575	0.4271	0.670
Type of surgery (subtotal gastrectomy)	29	72.5	0.005	2.526	0.012
Kattan score $\geq 100$	32	80	0.026	0.5097	0.611
Lymph nodes > 35	24	60	0.962		
Primary site			0.180	0.3756	0.708
Gastroesophageal junction	5	12.5			
Upper third	1	2.5			
Middle third	7	17.5			
Lower third	27	67.5			
Depth			0.017	0.2270	0.821
Mucosa	1	2.5			
Submucosa	5	12.5			
Muscularis propria	5	12.5			
Subserosa (suspected invasion)	11	27.5			
Serosa	3	7.5			
Adjacent structures	4	10.0			
Histological type (Lauren classification)			0.265	0.4180	0.677
Enteric	17	42.5			
Diffuse	13	32.5			
Mixed	10	25.0			
T status			0.006	0.6177	0.538
1a	0				
1b	5	12.5			
2	15	37.5			
3	12	30.0			
4a	4	10.0			
4b	4	10.0			
Stage AJCC/TNM			0.018	0.8390	0.403
IA	5	12.5			
IB	2	5.0			
IIA	6	15.0			
IIB	10	25.0			
IIIA	7	17.5			
IIIB	8	20.0			
IIIC	2	5.0			

AJCC: American Joint Committee on Cancer.

surgery is a complex procedure that leads to a high risk of morbidity and mortality [15]. Li *et al*[52] observed 30 d and 90 d mortality of 2.0% and 3.4%, respectively, in patients undergoing total gastrectomy for cancer. These data are consistent with what

**Table 6 Factors associated with surgical complications in univariate and multivariate analysis**

	Univariate analysis		Multivariate analysis		
	Number of cases	%	P value	T ratio	P value
Male sex	9	52.9	0.653	0.4193	0.675
Age > 65 yr	10	58.8	0.502	1.192	0.235
Type of surgery (subtotal gastrectomy)	10	58.8	0.595		
Kattan score $\geq 100$	14	82.3	0.116	0.08543	0.932
Lymph nodes > 35	16	94.1	0.002	3.222	0.001
Primary site			0.609		
Gastroesophageal junction	4	23.5			
Upper third	1	5.9			
Middle third	2	11.8			
Lower third	10	58.8			
Depth			0.045	0.8208	0.413
Mucosa	0				
Submucosa	2	11.8			
Muscularis Propria	2	11.8			
Subserosa (suspected invasion)	5	29.4			
Subserosa (certain invasion)	3	17.6			
Serosa	2	11.8			
Adjacent structures	3	17.6			
Histological type (Lauren classification)			0.817		
Enteric type	8	47.1			
Diffuse type	4	23.5			
Mixed type	5	29.4			
T status			0.054	1.102	0.272
T1a	0				
T1b	2	11.8			
T2	7	41.2			
T3	4	23.5			
T4a	1	5.9			
T4b	3	17.6			
Stage AJCC/TNM			0.019	0.8237	0.411
IA	1	5.9			
IB	0				
IIA	3	17.6			
IIB	5	29.4			
IIIA	3	17.6			
IIIB	4	23.5			
IIIC	1	5.9			

AJCC: American Joint Committee on Cancer.

is reported by other authors. Selby *et al*[53] reported data of 2.5% and 2.9% at 30 d and 90 d, respectively, while Pacelli *et al*[54] reported a mortality of 3.5% in 312 patients undergoing potentially curative gastrectomy for cancer. We observed a perioperative mortality rate of 3.8%. A higher mortality was observed in the group of patients aged > 65 years (8.7%) and in N + patients (6.2%).

The risk of postoperative complications is also high. Li *et al*[52] reports a complication rate of 43.9%, with a 14% incidence of severe (class III and class IV according to the Clavien-Dindo classification) complications. A severe complication after total gastrectomy is the anastomotic leak of the esophagojejunal anastomosis. In our experience, dehiscence occurred in 4 patients (2.1%), and was fatal in one case. Selby *et al*[53] and Pacelli *et al*[54] report an incidence of anastomotic dehiscence of 14.7% and 8.6% respectively. In our experience, all anastomotic leakages were identified in the early postoperative period, from day 4 to day 7, by performing routine upper GI contrast studies. The anastomotic leak leads to an increase in the duration of hospitalization, with increases ranging from 13 to 48 d of hospitalization [55]. Another severe complication is duodenal stump dehiscence. This complication occurred in 5 of our patients (2.7%), representing the cause of death in two of them. This complication also increased mortality in the literature[56]. We observed 2 cases of hemoperitoneum (1.0%) and 4 cases of pancreatic fistula (2.1%). These complications were fatal in the two cases of hemoperitoneum and in two of the 4 cases of pancreatic fistula. They were only observed in the patient group where more than 35 lymph nodes had been removed. In our series, mortality occurred only in the group of patients with a higher Kattan score. It seems likely that advanced stage tumors may alter the responsiveness of the patient, increasing the incidence of complications and mortality.

In our study, the overall incidence of surgery-related complications was 9.1%. As easy to predict, morbidity rate is higher in advanced tumors than in the earlier stage. The overall morbidity rate is higher in patients with Kattan score  $\geq 100$  ( $P = 0.02$ ) and in N + patients ( $P = 0.04$ ). Contrary to what has been observed in the literature, we documented a higher morbidity rate in patients undergoing subtotal gastrectomy (29 cases *vs* 11 cases after total gastrectomy -  $P = 0.006$ ). We believe that this is related to a higher mean age in patients who underwent subtotal gastrectomy ( $66.6 \pm 12.5$  years, range: 24-90) than in those who underwent total gastrectomy ( $63 \pm 12.1$  years, range: 30-84,  $P = 0.04$ ), and a higher mean Kattan score ( $125.1 \pm 46.7$  points, range 11-206) than in patients who underwent total gastrectomy ( $111.3 \pm 44.1$ , range 24-215,  $P = 0.03$ ). We observed a higher prevalence, without statistical significance ( $P = 0.2$ ), of patients with Kattan  $\geq 100$  points in the group undergoing subtotal gastrectomy (64 patients, 65.3%) compared to those undergoing total gastrectomy (49 cases, 55.6%). Regarding other parameters considered, such as the size of the tumor ( $4.1 \pm 2.0$  cm in subtotal gastrectomy *vs*  $4.6 \pm 2.6$  cm in total gastrectomy,  $P = 0.1$ ), the average number of positive lymph nodes ( $3.5 \pm 5.7$  in subtotal gastrectomy *vs*  $4.6 \pm 2.6$  in total gastrectomy,  $P = 0.1$ ) we did not find statistically significant differences. The number of lymph nodes removed was higher in patients undergoing total gastrectomy ( $40 \pm 10.4$ ) than in those undergoing subtotal ( $36.7 \pm 11.1$ ,  $P = 0.03$ ).

A higher incidence of surgical complications was observed in patients in whom more than 35 lymph nodes were removed. This data was confirmed in the univariate and multivariate analyses, where lymphadenectomy with the removal of more than 35 lymph nodes is the only factor that shows correlation with surgical complications. We have documented two cases of hemoperitoneum and 4 pancreatic fistulas, all in patients with spleen-preserving lymphadenectomy. Performing splenectomy for station 10 lymphadenectomy did not in our experience induce an increase in mortality and morbidity. These complications were found to be severe, as reported in the literature[26,57,58]. Many studies show that risk factors for the development of pancreatic fistula are the weight of the patient, the anatomy and texture of the pancreas, intraoperative trauma of the pancreas and the use of high-energy devices when performing lymphadenectomy[26,57].

Although we are aware that the Kattan nomogram was created to evaluate the long-term prognosis and survival of patients with gastric cancer undergoing R0 resection, we observed that the Kattan score, at the cut-off value used, is useful as a prognostic index even in the early postoperative phase. In our experience only patients with Kattan score  $\geq 100$  points died; a good correlation was also documented as far as the complication rate. Since Kattan takes into account, in addition to age, many characteristics of the tumor and the lymph node status, we have documented, as reported in the literature, that the incidence of mortality and major complications are observed with greater frequency in elderly patients, with more advanced and N + stage cancers. An intrinsic difficulty in using the Kattan score is the fact that the score itself is based on a

lot of histopathological information which are not always readily available.

All our patients underwent cholecystectomy. The procedure did not cause biliary complications. This aspect is controversial in the literature. In patients with a radical resection, when a D2 lymphadenectomy is performed and the duodenum is excluded in the intestinal reconstruction, cholecystectomy, considered by some to be a non-essential measure, is necessary to avoid gallstone formation and its complications. In this setting, we believe that prophylactic cholecystectomy is necessary for patients with a good cancer prognosis, as suggested by Pitt and Nakeeb[59]. Studies on the subject conclude that prophylactic cholecystectomy does not have a significant impact on the natural course of the disease[60]. However, it leads to a reduction in the number of biliary complications (which may affect up to 15% of the operated patients) and does not induce an increase in mortality and morbidity rates. In one study, a mortality rate of 1.8% was reported in the case of cholecystectomy performed during an intervention after a gastrectomy. Prophylactic cholecystectomy seems to be unnecessary only in cases where the continuity of the digestive tract involves the use of the duodenum[61]. It was found that the method used to restore intestinal continuity, with preservation of the duodenal transit or excluding the duodenum, is an independent risk factor for both the development of cholelithiasis ( $P = 0.018$ ) and cholecystitis and cholangitis ( $P = 0.006$ ). It has also been confirmed that in patients who develop cholelithiasis, the incidence of cholecystitis and cholangitis is particularly high when the duodenal transit is excluded (31.3%) compared to those with maintained duodenal transit (7.4%).

## CONCLUSION

It is fair to reiterate that gastric cancer surgery is a complex surgical procedure. Mortality and postoperative complications are linked both to the extent of gastric demolition and to lymphadenectomy. In our experience, the removal of more than 35 lymph nodes conditioned an increase in surgical complications, although it did not lead to an increase in mortality. Mortality was higher in elderly patients, N + patients and patients with advanced gastric cancer. These parameters (age, T status and N status) are included in the Kattan score, which can be useful, if the histopathological parameters can be obtained quickly, as a prognostic tool even in the early phase.

## ARTICLE HIGHLIGHTS

### Research background

Gastric cancer surgery is a complex procedure. Lymphadenectomy is essential for the surgical treatment of gastric cancer. Mortality and postoperative morbidity after gastric cancer surgery are not negligible.

### Research motivation

We investigated in a population of 186 patients with stomach cancer undergoing surgery with D2 lymphadenectomy which factors were related to postoperative mortality and morbidity.

### Research objectives

To evaluate the factors determining mortality and morbidity in a population of patients undergoing R0 resection and D2 lymphadenectomy for gastric cancer.

### Research methods

For each patient we calculated the Kattan's score. The following prognostic variables were assembled for use in validating the nomogram: age, sex, primary site (distal one-third, middle one-third, proximal one-third, and gastroesophageal junction), Lauren histotype (diffuse, intestinal, mixed), number of positive lymph nodes resected, number of negative lymph nodes resected, and depth of invasion as defined by the standard nomenclature.

### Research results

Perioperative mortality rate was 3.8% (7 patients); a higher mortality rate was observed in patients aged > 65 years ( $P = 0.002$ ) and in N+ patients ( $P = 0.04$ ).

Following univariate analysis, mortality was related to a Kattan's score  $\geq 100$  points ( $P = 0.04$ ) and the presence of advanced gastric cancer ( $P = 0.03$ ). Morbidity rate was 21.0% (40 patients). Surgical complications were observed in 17 patients (9.1%). A higher incidence of morbidity was observed in patients where more than 35 lymph nodes were harvested ( $P = 0.0005$ ).

### Research conclusions

Mortality and morbidity rate are higher in N+ and advanced gastric cancer patients. The removal of more than 35 lymph nodes does not lead to an increase in mortality.

### Research perspectives

An extended lymph nodes dissection in patients undergoing surgical treatment for gastric cancer is a safe procedure.

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