



## Original article

# Analysis of postoperative morbidity in patients with gastric adenocarcinoma treated using a protocol of preoperative chemoradiotherapy and surgery

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## A B S T R A C T

**Introduction:** The impact of neoadjuvant treatment on the postoperative complications in stomach cancer is a subject of controversy. The aim of this study is to analyse the post-surgical morbidity and mortality in a group of patients who were treated using a chemoradiotherapy protocol before surgery, as well as to identify the possible risk factors that may be associated with the development of complications.

**Material and methods:** Patients diagnosed with locally advanced gastric adenocarcinoma between June 2005 and June 2008 were operated on in our Centre after having followed a preoperative chemoradiotherapy protocol. Data on postoperative morbidity and mortality were collected retrospectively and the dependent variables associated with the patients, the type of intervention and the tumour characteristics were analysed.

**Results:** A total of 40 patients were evaluated. The overall morbidity and mortality was 32.5% (13 patients) and 2.5% (1 patient), respectively. The most frequent complications were pneumonia in 12.9% and sepsis due to the catheter in 9.7% of the patients. The risk factors for the development of complications were the body mass index (BMI, 25 kg/m<sup>2</sup>) and the inclusion of the pancreas and/or spleen in the resection.

**Conclusions:** Preoperative treatment with chemoradiotherapy in patients with locally advanced stomach cancer does not increase the incidence of post-surgical complication. The preoperative condition of the patient (BMI) and extending the surgery to the spleen and pancreas are prognostic factors of early postoperative complications.

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## Análisis de la morbilidad postoperatoria en pacientes con adenocarcinoma gástrico tratados según protocolo de quimiorradioterapia preoperatoria y cirugía

### R E S U M E N

#### Palabras clave:

Morbilidad

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**Introducción:** El impacto del tratamiento neoadyuvante sobre las complicaciones postoperatorias en el cáncer de estómago es motivo de controversia. El objetivo de este trabajo es analizar la morbilidad y la mortalidad postoperatoria en un grupo de pacientes a los que se les había aplicado un protocolo de quimiorradioterapia preoperatoria, así como identificar posibles factores de riesgo que se asocian al desarrollo de complicaciones.

**Material y métodos:** Entre junio de 2005 y junio de 2008, pacientes diagnosticados de adenocarcinoma gástrico localmente avanzado se intervinieron en nuestro Centro tras haber seguido un protocolo de quimiorradioterapia preoperatoria. Se recogieron prospectivamente los datos sobre morbilidad y mortalidad postoperatoria y se analizaron las variables dependientes relacionadas con los pacientes, con el tipo de intervención y las características tumorales.

**Resultados:** Se evaluaron 40 pacientes. La morbilidad y la mortalidad global fue del 32,5% (13 pacientes) y del 2,5% (un paciente), respectivamente. Las complicaciones más frecuentes fueron la neumonía en el 12,9% y la sepsis por catéter en el 9,7% de los pacientes. Los factores de riesgo para el desarrollo de complicaciones fueron el índice de masa corporal ( $>25 \text{ kg/m}^2$ ) y la inclusión en la resección del páncreas o del bazo.

**Conclusiones:** El tratamiento preoperatorio con quimiorradioterapia en pacientes con cáncer de estómago localmente avanzado no incrementa la incidencia de complicaciones postoperatorias. La condición preoperatoria del paciente (índice de masa corporal) y la extensión de la cirugía del bazo y del páncreas son factores pronósticos de complicaciones postoperatorias precoces.

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## Introduction

Gastric cancer accounts for 9.9% of all cancers diagnosed worldwide and it is the cause of 12.1% of cancer-related deaths.<sup>1</sup> Although the incidence of gastric cancer is decreasing, it continues to be—globally—the second cause of death specifically caused by cancer.<sup>2</sup> Surgical treatment continues to be the cornerstone of treatment for this disease, obtaining 5-year survival rates of 15% to 35%.<sup>1</sup> Our current understanding of the disease continues to improve, with respect to aspects such as how invasive surgery should be, the value of lymphadenectomy, the optimal chemotherapy regimen and sequence, and the impact of new radiation techniques, whether they are administered as neoadjuvant or adjuvant treatment.

The potential advantages derived from combined multimodal treatment, as opposed to surgery as the only form of treatment, are better local control of the disease and increased global survival.<sup>3-5</sup> Preoperative treatment appears to offer advantages in comparison to postoperative treatment, as it reduces tumour size, facilitates R0 resection and provides prognostic data on tumoral response. Another advantage is that tissues are more sensitive to radiotherapy when it is applied before the surgical intervention.<sup>6,7</sup> Furthermore, preoperative treatment is better tolerated when patients have not yet been subjected to the aggressive effects of surgery.

In recent decades there have been reports of significant

reductions in tumoral stage (*downstaging*), as a result of the application of preoperative chemoradiotherapy, in patients with carcinoma of the stomach or the gastro-oesophageal junction.<sup>6-8</sup> Despite these claims, the influence of this therapeutic option on postoperative morbidity and mortality has not been entirely clarified, given that there are few publications which specifically address this issue.<sup>8</sup>

The aim of this study is to analyze the frequency and nature of postoperative complications in patients diagnosed with locally advanced gastric adenocarcinoma and treated with preoperative chemoradiotherapy, and to identify possible risk factors associated with postoperative complications.

## Patients and methods

### Selection of patients

From June 2006 to June 2008 patients diagnosed with locally advanced gastric adenocarcinoma were evaluated and treated using a preoperative chemoradiotherapy protocol at the Clínica Universidad de Navarra. The same multidisciplinary team of oncologists, surgeons, and radiotherapists attended all of these patients.

The inclusion criteria for this study were a histological diagnosis of adenocarcinoma of the stomach or the gastro-oesophageal junction, in which the study of the extension of

the disease, in accordance with the TNM system classification,<sup>9</sup> revealed tumoral infiltration beyond the muscular layer (cT3), with or without suspected cN0-N+ lymph gland metastasis, in the endoscopic ultrasound scan (EUS). Patients with Eastern Cooperative Oncologic Group Performance Status<sup>10</sup> grades 0-2 and patients who had not previously received chemotherapeutic treatment or radiotherapy of the abdominal region were also included. Creatinine clearance values above 50 mL/min, liver enzyme levels no higher than 3 times control values, and also an adequate bone marrow reserve, defined as a leukocyte count in excess of  $3 \times 10^9/L$  (absolute granulocyte count higher than  $1.5 \times 10^9/L$ ) and platelet count higher than  $75 \times 10^9/L$ ) were used as additional inclusion criteria.

Patients with gastric adenocarcinoma and distant metastasis (M1), positive peritoneal cytology, or carcinomatosis were excluded from the study. Patients with serious comorbidity (cardiovascular, cerebrovascular, or psychiatric disease) were also excluded because it was thought that they would be unable to comply with the treatment protocol. All the patients signed the informed consent prior to treatment and the study was approved by the Ethics Committee of the Hospital.

The diagnosis of gastric adenocarcinoma was confirmed by upper endoscopy and biopsies, while computerized axial tomography of the chest and abdomen and EUS were used to establish the clinical TNM of the disease. Before initiating the radiotherapy treatment a diagnostic laparoscopy was performed on all the patients in order to rule out the possibility of disseminated abdominal disease.

In all cases the clinical data was collected prospectively and stored in a database, paying special attention to patient characteristics (age, sex, body mass index [BMI], and the index of the American Society of Anesthesiologists [ASA]),<sup>11</sup> as well as the characteristics of the surgical procedure (type and duration of surgery and blood transfusion), radiotherapy, and the tumour (extension study in accordance with the TNM classification), and its localization.

#### Preoperative treatment

##### 1. Induction chemotherapy

All the patients received 2 induction chemotherapy cycles and followed a docetaxel (60 mg/m<sup>2</sup>), oxaliplatin (85 mg/m<sup>2</sup>), and capecitabine (650 mg/m<sup>2</sup>) regimen. A full medical examination was conducted and a blood cell count was obtained on the first day of each cycle.

##### 2. Concurrent chemoradiotherapy

###### a) Radiotherapy

Three weeks after completing the induction chemotherapy treatment and after performing a diagnostic laparoscopy, concurrent chemoradiotherapy was administered. Radiotherapy was applied in accordance with the recommendations of Ajani et al,<sup>6</sup> including the stomach, any perigastric extension and the locoregional lymphatic drainage system in the volume to be irradiated. The technique employed 2 or 3 fields and high energy photons (15 MV) generated by a linear accelerator until a total dose of 45 Gy (daily fractions of 1.8 Gy during a period of 5 weeks) was delivered.

###### b) Chemotherapy

The following chemotherapy regimen was scheduled in combination with radiotherapy: oxaliplatin (50 mg/m<sup>2</sup> during weeks 1, 2, 4, and 5), capecitabine (650 mg/m<sup>2</sup> from Monday to Friday, concurrent with radiotherapy), and docetaxel (depending on the dose delivered, escalating during weeks 1, 2, 4, and 5).

#### Surgical treatment

Five weeks after completing the chemoradiotherapy treatment and prior to surgery, CAT scans of the chest and abdomen and upper EUS were performed again to re-evaluate the clinical stage of tumours and the response to treatment. The same group of surgeons performed all the surgical interventions. The type of surgery depended on the localization and extension of the tumour. Subtotal gastrectomy was performed in the case of distal tumours. In the case of proximal localizations, total gastrectomy or oesophagogastrrectomy was performed, using the Ivor Lewis technique (oesophagectomy and proximal gastrectomy), where there was infiltration of the distal oesophagus. A bloc resection of adjacent organs was also performed when they were found to be locally infiltrated. A D2 lymphadenectomy was conducted in most cases; the left gastric vessels were sectioned at their source and a dissection of the ganglia in the perigastric region and around the celiac trunk and its main branches was performed. In addition, the mediastinic ganglia—beneath the azygous vein—and paraoesophageal ganglia—were dissected at the same time as the oesophagogastrrectomy—.

#### Histopathological study

The same pathologist carried out the pathological examination of the surgical biopsy samples and classified them in accordance with the TNM classification system.<sup>9</sup> A standard analysis of all the surgical pieces was performed and the pathological findings were categorized after the chemoradiotherapy, on the basis of an estimation of the amount of residual cancer in relation to the extension of the initial tumour. Tumoral response was classified using the Becker criteria.<sup>12</sup>

In the cases in which the pathological evaluation revealed the implication of lymph glands or advanced stages of the disease, postoperative treatment based on 3 cycles of docetaxel, oxaliplatin, and capecitabine was prescribed.

#### Complications

The postoperative complications were grouped as follows: wound complications (infection, seroma, or abscess), intra-abdominal abscess (confirmed by radiological images), anastomotic leakage (regarded as such when there were clinical manifestations which required treatment), postoperative haemorrhage, pancreatic leakage (diagnosed on the basis of high levels of amylase in the drainage system), general complications (cardiovascular complications, catheter sepsis or thrombosis), and pulmonary complications (confirmed by radiology). Operative mortality was defined as mortality

which occurred during the first 30 days after surgery or during the hospital stay.

### Statistical analysis

Throughout the entire study the same surgeon supervised the collection of data. The categorical variables were analyzed using contingency and  $\chi^2$  tables or Fisher's exact test, depending on each individual case. Continuous variables were analyzed using the Student *t* test. Correlations between independent variables and complications were analyzed by logistic regression. *P* values lower than .05 were regarded as statistically significant. The SPSS program (version 14.0) was employed for the data analysis (SPSS, Chicago, Illinois).

## Results

### Patient characteristics

During the period from June 2006 to June 2008 interventions were performed on 69 patients diagnosed with gastric

chemoradiotherapy protocol and 3 patients were excluded from the study (2 owing to progression of the disease during the treatment and 1 who failed to agree to the intervention). Table 1 shows the characteristics of the study patients.

### Characteristics of the surgical procedure

In a similar way, Table 1 shows the types of intervention which were performed. Total gastrectomy was performed in 19 patients (47.5%); in 1 case oesophagogastrectomy had to be performed using the Ivor Lewis technique, owing to tumoral invasion of the distal oesophagus. In 14 of these gastrectomy cases (35%) the tumour was located at the gastrooesophageal junction. Subtotal gastrectomy was performed on 10 patients (25%) and another 10 patients (25%) required an extended gastrectomy, involving the spleen or pancreas, owing to tumoral invasion. The average duration of the intervention was 180 min (range, 40-370). The average number of resected lymph ganglia was 16 (range, 2-59) and D2 lymphadenectomy was performed in 90% of the patient series. In 23 cases the patients were admitted to the intensive care unit after surgery and in 5 cases (12.5%) the patients required a blood transfusion, there being an estimated average blood loss during the operation of 300 mL (range, 50-1700). R0 resection was performed in 36 cases (90%), R1 palliative resection in 3 cases (7.5%), and an R2 palliative resection in 1 case (2.5%). In 55% of the cases a greater pathological response was detected (according to Becker's criteria) in the anatomopathological analysis of the surgical samples.

### Complications

Global morbidity was 32.5% and postoperative complications occurred in 13 patients. The complications which were found are described in Table 2. The 2 most common complications were pneumonia and intravenous catheter-related infection. A statistically significant correlation between obesity and wound infection was identified (*P*=.027). Interventions were repeated in 3 patients (8.8%) and the average hospital stay was 10 days (range, 5-33). One patient died during the postoperative period (2.5%). The cause of death was pulmonary failure secondary to a massive aspiration after endoscopy.

**Table 1 – Patient characteristics**

Number of patients	40	100%
Age		
<50 years	11	27.5
51-65 years	19	47.5
>65 years	10	25.0
Sex		
Male	32	80.0
Female	8	20.0
ASA		
I+II	13	32.5
III+IV	27	67.5
Tumoral localization		
Proximal	16	40.0
Middle	6	15.0
Distal	6	15.0
Diffuse	12	30.0
Clinical TNM stage		
0	—	—
IA	—	—
IB	—	—
II	5	12.5
IIIA	17	42.5
IIIB	1	2.5
IV	17	42.5
Type of surgery		
Subtotal gastrectomy	10	25.0
Total gastrectomy	19	47.5
Gastrectomy+splenectomy	10	25.0
Gastrectomy+pancreatectomy	1	2.5

ASA indicates American Society of Anesthesiologists; TNM, tumour, node, metastasis system.

**Table 2 – Surgical morbidity and mortality**

Complications	No. of patients (40)	%
No. of patients with complications	13	32.5
Wound infection	1	3.1
Anastomosis fistula	3	7.5
Intra-abdominal abscess	2	5.0
Pancreatic fistula	1	2.5
Postoperative haemorrhage	2	5.0
General complications		
Catheter sepsis	4	9.7
Thromboembolism	1	2.5
Other (urinary, iliac, or cardiac complications)	2	5
Pneumonia	5	12.9
Mortality	1	2.5

**Table 3 – Univariate analysis**

	No. of patients	No. of patients with complications	%	P <sup>a</sup>
Sex				
Female	8	2	25	.479
Male	32	11	34.4	
Age				
<65	31	10	32.3	.624
≥65	9	3	33.3	
BMI				
<25	12	4	33.3	.039
≥25	18	8	66.7	
ASA				
I/II	13	3	23.1	.305
III/IV	27	10	37	
Tumoral localization				
Proximal	16	5	31.3	.110
Middle	5	2	40.0	.510
Distal	7	3	42.9	.690
Diffuse	12	3	25.0	
Type of surgery				
Total/subtotal gastrectomy	30	7	23.3	.042
Gastrectomy+pancreas/spleen	10	6	60	
Related surgery				
No	23	6	27.3	.283
Yes	17	7	41.2	
Intervention duration				
<180 min	22	7	31.8	.592
≥180 min	18	6	33.3	
Blood transfusion				
No	35	11	31.4	.531
Yes	5	2	40	

ASA indicates American Society of Anesthesiologists; BMI, body mass index (kg/m<sup>2</sup>).  
<sup>a</sup>χ<sup>2</sup> test.

The results of the univariate and multivariate analysis correlated against the variables associated with patients, surgical intervention and tumoral localization are shown in Table 3 and Table 4. Of all the variables, the only ones identified in this study as possible risk factors which were unrelated to

the risk of complications were the extension of surgery of the pancreas or spleen and a BMI higher than 25 kg/m<sup>2</sup>.

## Discussion

Postoperative complications secondary to gastric surgery are common and in the medical literature their incidence ranges from 19% to 63%, depending on the population which is selected, surgical experience, the interventions which are performed and the criteria used to diagnose complications.<sup>8,13-18</sup> Although some surgeons believe that neoadjuvant treatment increases the incidence of postoperative complications in cases of gastric cancer, there is no evidence available on this issue and there is only one study which specifically analyzes the influence of chemoradiotherapy on postoperative morbidity and mortality.<sup>8</sup>

The percentage of postoperative complications found in this study was 32.5%, which matches with our previously

**Table 4 – Risk factors identified by multivariate analysis**

	OR	CI (95%)	P
BMI			
<25	1	1.18–4.58	.015
≥25	2.32		
Type of surgery			
Total/subtotal gastrectomy	1	1.29–2.94	.026
Gastrectomy+pancreas/spleen	1.32		

BMI indicates body mass index (kg/m<sup>2</sup>), CI, confidence interval; OR, odds ratio.

published findings in patients treated with surgery alone<sup>19</sup> and those of Fujitani et al<sup>8</sup> involving a group of patients with similar characteristics and a preoperative chemoradiotherapy protocol. Consequently, these results demonstrate that, as well as improving results in the long term as far as survival and local relapse are concerned,<sup>3,7,20</sup> neoadjuvant treatment does not increase the rate of early postoperative complications following surgery.

And, when we analyze the frequency of major postoperative complications of surgery in patients who have received preoperative chemoradiotherapy, we find that the results match with those previously published by centres with experience in Western countries and the percentage for anastomotic leakage is 1.2%-8.1%; 1.8%-4.2% for intra-abdominal abscess; 0.2%-5.3% for pancreatic fistula; 1.1%-3.9% for wound infection and 1.2%-1.9% for postoperative intra-abdominal haemorrhage.

It is worth noting that most of the complications responded well to medical treatment. The main causes of reintervention were intra-abdominal abscess as a result of anastomotic fistula and intra-abdominal haemorrhage. All these patients recovered satisfactorily, with no cases of postoperative mortality, although for some authors the need for reintervention, owing to an oesophago-jejunal fistula or an intra-abdominal abscess, is a factor which increases postoperative mortality significantly.<sup>18</sup>

Reviews of non-randomized studies<sup>21</sup> indicate that the evolution of patients with anastomotic leakage is better when the treatment of this complication is conservative and percutaneous drainage is employed. Whatever the case, in view of our results, it does not seem that neoadjuvant chemoradiotherapy treatment significantly increases the risk of fistula (7.5%). Although we are aware of the limitations of this study, our findings support the evidence found in the medical literature.<sup>8,22,23</sup>

So far the postoperative complications in gastric cancer patients who have undergone a D2 lymphadenectomy have been investigated in research studies. In all these patients pancreatic resection associated with gastric surgery was the factor which was most prominently linked to complications.<sup>24,25</sup> Furthermore, some studies conducted in the 1990s demonstrate that splenectomy showed a negative correlation with postoperative morbidity and mortality.<sup>26,27</sup> This was later confirmed in 2 randomized European studies which compared D1 and D2 lymphadenectomy.<sup>24,28</sup> In relation to this, in a study published by our group we failed to find significant differences in terms of postoperative complications when limited D1 lymphadenectomy was compared with the more extensive D2 lymphadenectomy, which improves the results in terms of survival for the D2 intervention.<sup>29</sup>

At present, it is not clear whether patients with advanced stage tumours benefit more from preserving their spleen intact or from a splenectomy combined with distal pancreatectomy as part of a block resection, as some surgeons have proposed. In this study, pancreatectomy and splenectomy proved to be risk factors which were not directly linked to complications, thereby confirming our previous findings published in 2006 in 434 gastric cancer patients treated with surgery alone.<sup>19</sup> In 10 patients treated with preoperative chemoradiotherapy

it was necessary to perform a partial splenectomy or pancreatectomy due to tumoral invasion.

Given the lack of evidence on the improvement in survival rates in studies published in Western countries and the significant increase in complications derived from this type of intervention (such as pancreatic fistula, intra-abdominal abscess, and haemorrhage), this procedure is not recommended as standard treatment for advanced tumours. In recent years we have tended to reduce the frequency of extended gastrectomies, despite the presence of tumours at a clinically advanced stage in this study. This is supported by the good pathological response found in patients who received preoperative chemoradiotherapy.

Factors related to patient characteristics such as age, sex, ASA anaesthetic risk, tumoral localization, and clinical TNM stage proved to be irrelevant in the multivariate study. The only factor associated with a greater risk of postoperative complications was a BMI higher than 25 kg/m<sup>2</sup>. This result also confirms our findings in patients treated with surgery alone<sup>19</sup> and those published by other authors.<sup>30</sup> Furthermore, it is important to point out that we found a significant link ( $P=.027$ ) between obesity and wound infection (seroma and infection), probably owing to metabolic factors or diabetic comorbidity.

In summary, the most common complications encountered in operated stomach cancer patients were general complications, such as pneumonia and catheter-related infections, which were not specifically related to surgery. The use of chemoradiotherapy in selected patients with locally advanced gastric adenocarcinoma is not associated with a higher percentage of initial postoperative complications. The preoperative status of patients, especially their BMI, and more invasive surgery involving the pancreas and spleen are the factors which play the most decisive role in postoperative complications, so that decisions about the type of surgery which should be performed and better preoperative control of dependent patient variables are directly related to improvements in results.

## Conflicts of interests

The authors affirm that they have no conflicts of interest.

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