Relationship between postoperative complications and survival after gastrectomy for cancer

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BACKGROUND: *Surgical resection remains the main curative treatment for gastric cancer but is still affected by high postoperative morbidity and mortality rates, especially in Western countries.*
MATERIALS AND METHODS: *We've analyzed patients treated for gastric cancer at our Operative Unit of ent, extent of lymphadenectomy and survival. General Surgery and Organ Transplantation of the University Hospital of Parma from January 2006 till December 2010, relating the occurrence of eventual complications to sex, age at diagnosis, definitive histological examination, type and duration of surgical treatment.*
RESULTS: *The surgically treated cases were 152 (30.4 gastrectomies per year on average). 62 patients developed at least one adverse event during the postoperative period, reaching 108 total events. Among these, 71 were minor complications (grade I-II in Clavien-Dindo's classification), while 26 were major ones (grade III). Postoperative mortality affected 8 patients (5.3%). Data analysis did not stress any statistically significant correlation between the valued variables and the global incidence of complications. For severe ones, some risk factors emerged such as the type of gastrectomy, the execution of a multi-visceral resection and the operative time. Five-year overall survival has been 36.7%, lower in patients with severe complications (29%) when compared to patients without severe complications (38%). Radicality of operation, the lymph node involvement and the occurrence of severe complication emerged as significant prognostic factors for five-year overall survival.*
CONCLUSIONS: *Surgery is still the mainstay of treatment for gastric cancer and the only one able to grant a curative therapy. When performed in high-volume centres, with more than 20 gastrectomies per year, it represents a safe treatment, affected by low mortality. Attention must be paid to careful preoperative selection, to treatment of pre-existent comorbidities, to plan a therapeutical strategy to minimize surgical stress, to postoperative monitoring and to managing complications', as they're able to impact not only low-term outcomes but also overall and disease-free survival. The poor prognosis for these patients is mainly related to advanced stage at presentation, thus confirming the need to increase early diagnosis in order to detect in larger percentages the tumor in its early stage.*

KEY WORDS: Complications, Gastrectomy, Gastric Cancer, Survival

Introduction

Gastric carcinoma (GC)accounts for over 95% of all malignant gastric neoplasms. With more than 930.000 new cases and 700.000 deaths per year, it is the world's fourth most common cancer and the second leading cause of death from neoplasia [1]. Italy is placed in the middle, with attested values ranging from an average 38 cases per 100000 inhabitants for males and 25 cases per 100000 inhabitants for females. In Italy areas with highest incidence are Lombardy, Tuscany, Lazio and Emilia Romagna [2].

Gastric cancer is showing a decreasing trend in both occurrence and mortality among all the industrialised countries (excepting Japan) during the last few decades. Such decrease affects especially tumors located in the

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antrum; improved quality of life, greater varability of diet , better food preservation and the reduced prevalence of Helicobacter Pylori infection explain the decrease incidence of Gastric Cancer.

7th Edition of TMN UICC/AJCC is the validated staging system of Gastric Cancer. Five-year survival rate is 70,8% for stage IA cancers and decreases progressively with the subsequent stage increase till reaching a minimum of 4% for stage IV cancers [3].

The depth of cancer invasion (T) and lymph nodes involvement are the most relevant prognostic factors [4]. Lymph Node Ratio(LNR) has recently been proposed as a new independent prognostic factor. Lymph Node Ratio defines the ratio between the lymph nodes which have been found positive for metastases and the total number of removed lymph nodes [5]. The main advantages are a less strict dependence on the number of retrieved lymph nodes and the rare observation of the so called "stage migration" phenomenon. As suggested by a recent study run by our Operative Unit, the Lymph Node Ratio could be more sensitive than the number of removed lymph nodes in identifying patients' classes with comparable life expectancy [5]. Among the analysed data, comprising cases of gastric carcinoma treated at the Operative Unit of General Surgery and Organ Transplantation of the University Hospital of Parma, the patients classified as LNR1 showed a statistically significant higher survival rate when compared to patients classified as LNR>1 [5].

In USA and Europe, curative resections are only possible on 50-60% of patients with newly diagnosed gastric tumor. For advanced stages II and III, even after resection with free margins, the risk of recurrence is high. Adjuvant chemotherapy, whether associated or not with locoregional radiotherapy, is the most commonly pursued strategy to reduce the recurrence risk and increase the rate of potentially curative resections. A meta-analysis by the "Global Advanced/Adjuvant Stomach Tumor Research International Collaboration Group" has confirmed a decrease in five-year mortality in patients undergoing adjuvant therapy in comparison to patients treated only with surgery [6].

The rationale for choosing a neo-adjuvant treatment stands in the purpose of precociously attacking eventual distant micro-metastases and increasing the resectability rate through a downstaging of the primary cancer [7].

MAGIC (MRC Adjuvant Gastric Infusional Chemotherapy) study, conducted by the United Society of Surgical Oncology, has randomized 503 patients with either gastric or gastroesophageal-junction cancer, showing a decrease in size of the tumor and its downstaging and also stressing a 13% advantage in survival by using perioperative chemotherapy versus surgery alone [8]. Morbidity and postoperative mortality have proved to be comparable in both groups (46% and 6% in preoperatively treated patients versus 45% and 6% in patients undergoing surgical treatment alone), this result being substantially confirmed by other studies as well [9,10]. Up to 35% patients undergoing postoperative complications can suffer a delay in the administration of adjuvant treatment or be totally excluded from it [11] with negative impact on both overall and disease-free survival. On the basis of this evidence, Badgwell et al. suggest neoadjuvant chemotherapy, whether or not associated with radiotherapy, for completing the entire cycle before the actual surgical treatment [10,2].

Materials and Methods

We've analyzed patients treated with gastric resection or total gastrectomy for gastric cancer at the Operative Unit of General Surgery and Organ Transplantation of the University Hospital of Parma.

We examined patients ranging from January 2006 to December 2010. The data regarded sex, age at diagnosis, type of surgical treatment, definitive histological

Table I - *Clavien-Dindo Classification of Surgical Complications.*

Grade	Definition
GRADE I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
GRADE II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications Blood transfusions and total parenteral nutrition are also included
GRADE III	Requiring surgical, endoscopic or radiological intervention
IIIa	Intervention not under general anesthesia
IIIb	Intervention under general anesthesia
GRADE IV	Life-threatening complication requiring IC/ICU management
IVa	Single organ dysfunction
IVb	Multiorgan dysfunction
GRADE V	Death of the patient.

examination, tumor stage and occurrence of eventual complications. These were in turn classified according to severity using Clavien-Dindo classification [12] (Table I).
Complications can be divided into local and systemic ones.
Local complication include more frequently: leak, dehiscence, anastomotic stenosis, fluid collection or abscess, intestinal obstruction, prolonged postoperative ileus, intra-abdominal and intraluminal bleeding, surgical wound problem (infection, dehiscence, hematoma, seroma).
Systemic complications can involve: respiratory system (atelectasis, pleural effusion, empyema, pneumonia, pneumothorax), cardiovascular system (myocardial infarction, angina pectoris, arrhythmia, TVP), kidneys (acute kidney injury), hepatobiliary system (rising indices of hepatic cytolysis, acute cholecystitis), pancreas (acute pancreatitis) [13,14].
The occurrence of postoperative complications not only affects the quality of life, it could as well increase the risk of recurrence, thus jeopardizing short and long-term survival [15-18].
We compared patients according to operative time, to gastric site of the neoplasia, to either elective or urgent character of surgery, to the extent of lymph node dissection, to possible multi-visceral resections and to survival in order to identify factors influencing surgical morbidity and mortality.
The data have been statistically analysed through using Chi-square test and logistic regression for multivariate analysis of factors; $p<0.05$ was considered statistically significant.
The survival curves were estimated according to the Kaplan-Meier method. We used Cox proportional hazard model to analyze factors associated with mortality.

Results

From January 2006 to December 2010, 152 patients underwent surgery for Gastric Cancer at the Operative Unit of General Surgery and Organ Transplantation of the Parma Academic Hospital. Among them 94 were male and 58 female, with a M:F ratio of 1,6. Mean age resulted being 73.1 years (range 43-90 y.), lower in men (72,5 years) than in women (74,1), more than 80% being older than 65 years. 69 (45,4) total gastrectomies and 67 (44,1%) gastric resections were performed. Mean age was lower for patients undergoing total gastrectomy (68,4) when compared to the others (77,4). In 10 cases a remnant gastrectomy was required for treating a carcinoma occurred in gastric stump. In the remaining cases a gastro-entero-anastomosis was performed as palliative measure. 66 cases required an extended resection because of direct infiltration of adjacent organs. Spleen was removed in 19 cases. Pancreas was resected in 3 cases. 9 procedures were performed in urgency, in 2 of them the patient died within 30 days after surgery. The average number of retrieved lymph nodes was 26,8 after total gastrectomy and 15,4 after subtotal resection.
Mean operative time was 208,3 minutes, longer for total gastrectomy (234.2 min.) when compared to partial resection (178,3 min.).
According to pathologic examination, the diffuse histotype (in Lauren's classification) was detected in 41 cases (27%), the intestinal histotype in 77 cases (50,7%), the mixed type in 15 cases (9,9%). 19 cases were not classified according to Lauren. In 27 cases an Early Gastric Cancer was found (17,8%). In 67 (44,1%) cases, the tumor was localized in the lower third, in 40 (26,3%) in the middle third and in 26 (17,1%) in the upper third. The most frequent cancer site resulted being the antral or antro-piloric one. 10 carcinomas arised on the gastric stump (6,6%). 6 cases (3,9%) were found with Linitis Plastica.
All patients were staged following the Seventh Edition of the AJCC Cancer Staging System (2010). 37 patients presented disease at stage I (24,3%), 28 at stage II (18,4%), 61 at stage III (40,1%) and 18 at stage IV (11,8%). 1 single case showed stage 0 disease (0,7%).
62 patients (40,8 %) developed complications during the postoperative period, reaching a total of 108 events. Among these, 71 were minor complications, thus handled with conservative treatment (grade I-II according to Clavien-Dindo's classification, usually referred to as minor complications), 26 required a surgical, endoscopic or radiological treatment (grade III, usually designated as major or severe complications) (Table II).

Table II - *Type and severity of complications*

		Severity grade of Complication		
	No.	**I-II**	**III-IV**	**V**
Local Complications				
Anastomotic stenosis	19	18	1	0
Abscess and fluid collection	14	8	6	0
Intestinal motility disorders	12	10	2	0
Anastomotic leakage	10	2	4	4
Esopagheal dyskinesia	7	7	0	0
Anastomotic dehiscence	4	0	2	2
Peritonitis	4	2	1	1
Gastric stasis, emesis	4	4	0	0
Wound problem	3	2	1	0
Bleeding	2	0	1	1
Splenic Infarction	1	1	0	0
Systemic Complications				
Respiratory	22	14	7	1
Sepsis	2	0	1	1
Pulmonary embolism	2	2	0	0
Fever	1	1	0	0
Multi-organ failure	1	0	0	1
Total	108	71	26	11

Table III - *Univariate analysis for factors related to postoperative morbidity and mortality.*

Variable	Patients	Overall Cx 1		Severe 2 Cx 1		Mortality	
	n°	n° (%)	P	n° (%)	P	n° (%)	P
Sex			ns		ns		ns
Male	94	35 (37,2)		18 (19,1)		6 (6,4)	
Female	58	27 (46,6)		9 (15,5)		2 (2,1)	
Age			ns		ns		ns
< 75	78	30 (38,5)		16 (20,5)		2 (2,6)	
≥ 75	74	32 (43,2)		11 (14,9)		6 (8,1)	
Location			ns		ns		ns
Proximal	76	35 (46,1)		16 (21,1)		6 (7,9)	
Distal	67	22 (32,8)		9 (13,4)		2 (3)	
Histologic Type			ns		ns		ns
Intestinal	77	28 (36,4)		11 (14,3)		4 (5,2)	
Diffuse/Mixed	56	23 (41,1)		10 (17,9)		2 (3,6)	
TNM Stage			ns		ns		ns
I-II	66	23 (34,8)		10 (15,2)		2 (3)	
III-IV	79	36 (45,6)		15 (22,7)		5 (6,3)	
Type of Resection			ns		**0,048**		ns
Subtotal	67	23 (34,3)		7 (10,5)		2 (3)	
Total	69	30 (43,8)		16 (23,2)		6 (8,7)	
Type of Reconstruction			ns		ns		ns
Billroth II	42	15 (35,7)		6 (14,3)		3 (7,1)	
Roux	105	45 (42,9)		20 (19)		4 (3,8)	
Anastomotic technique			ns		ns		ns
Hand sutures	43	15 (34,9)		5 (11,6)		1 (2,3)	
Staplers	89	42 (47,2)		19 (21,3)		5 (5,6)	
Combined Resection			ns		**0,024**		ns
Yes	66	31 (47)		17 (25,8)		6 (9,1)	
No	86	31 (36)		10 (11,6)		2 (2,3)	
Radicality			ns		ns		ns
Yes	122	49 (40,2)		20 (16,4)		4 (3,3)	
No	30	13 (43,3)		7 (23,3)		4 (13,3)	
Margin Status			ns		ns		ns
Clean	136	56 (41,2)		22 (16,2)		6 (4,4)	
Infiltrated	10	3 (30)		3 (30)		1 (10)	
Operative Time			ns		**0,0196**		ns
< 200 Min	76	26 (34,2)		8 (10,5)		4 (5,3)	
≥ 200 Min	76	36 (47,4)		19 (25)		4 (5,3)	
N° Retrieved LN			ns		ns		ns
< 16	59	22 (37,3)		10 (17)		3 (5,1)	
≥ 16	85	35 (41,2)		15 (17,7)		4 (4,7)	
Metastatic LN			ns		ns		ns
Yes	96	40 (41,7)		20 (20,8)		6 (6,3)	
No	48	17 (35,4)		5 (10,4)		1 (2,1)	
Urgent surgery			ns		ns		**0,02**
Yes	9	6 (66,7)		2 (22,2)		2 (22,2)	
No	143	56 (39,2)		25 (17,5)		6 (4,2)	

ns not statistically significant; [1] complications; [2] complications ranking grade III or higher according to Clavien-Dindo's classification

Table IV - *Multivariate analysis for factors related to severe complications*

Variable	Odd Ratio	95% CI	P
Type of Resection	1,066	0,394 – 2,885	0,9
Combined Resection	2,346	0,922 – 5,969	0,064
OperativeTIme	2,528	0,947 – 6,744	0,074

CI confidence interval

Table V - *Characteristics of patients died within five years after surgery*

Variable	Patients	Death within 5 years
	n°	n° (%)
Sex		
Male	81	47 (58)
Female	54	39 (72)
Age		
< 75	70	41 (58,6)
≥ 75	65	45 (69.2)
Histologic Type		
Intestinal	71	38 (53.5)
Diffuse/Mixed	50	37 (74)
Depth of invasion		
pT 1-2	44	14 (31.8)
pT 3-4	86	68 (79.1)
Lymph node involvement		
pN 0-1	67	28 (41.8)
pN 2-3	63	54 (85.7)
TNM Stage		
I-II	61	22 (36.1)
III-IV	69	60 (86.9)
Type of Resection		
Subtotal	63	36 (57.1)
Total	62	44 (70.9)
Combined Resection		
Yes	54	42 (77.8)
No	81	44 (54.3)
Radicality		
Yes	111	62 (55.9)
No	24	24 (100)
Margin Status		
Clean	123	75 (61)
Infiltrated	8	7 (87.5)
Severe Complications		
Yes	17	13 (76.5)
No	118	71 (60.2)

There were 80 local complications: anastomotic stricture was the most frequent [19], abscesses and intra-abdominal fluid collections [14], intestinal motility disorders (prolonged post-operative ileus, obstruction) [12] and anastomotic leakages [10]; 18 were ranked as grade III.

Re-laparotomies were performed in 8 pts.; in one case, death occurred after the re-operation.

Systemic complications recorded were 28: the most frequent ones being respiratory complications [22], particularly pleural effusion.

Postoperative mortality affected 8 patients (5.3%): 2 cases because of the duodenal stump dehiscence, 4 cases because of the development of anastomotic leak, 1 case for postoperative multi-organ failure. In the one remaining case, death occurred following pneumonia.

These data did not stress any statistically relevant connection between the variables analyzed consideration and the overall incidence of complications. The analysis showed that patients with morbidity ranking equal or higher than grade III has marked out 3 operative variables as significant: type of gastrectomy(p=0.048), multi-visceral resection (p=0.024) and the operative time (p=0.0196) were relevant variables in the postoperative morbidity.

30-day postoperative mortality rsulted significantly related to surgery performed in urgency (p=0.02 (Table III). Multivariate analysis failed to find any independent risk factor for postoperative morbidity (Table IV).

Five-year overall survival rate was 36.7%. Overall survival was 29% in patients with the ssevere postoperative complications versus 33% in pts.

The highest number of deaths occurred within the 24th month from surgery (59% of patients with severe complications versus 47% of patients without severe complications) (Fig. 1). Table V shows the characteristics of patients who did not survive five years after surgery.

Univariable and multivariate analysis showed that lymphnode involvement radicality and postoperative complications were significant prognostic factors (p<0.05). (Table VI).

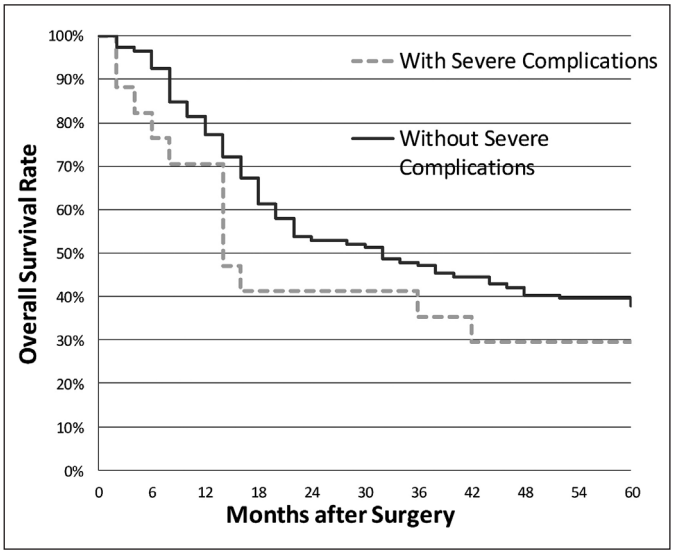

Fig. 1: 5-year Overall Survival Rate in patients with and without severe complications.

Table VI - *Univariate and multivariate analysis of prognostic factors for five-year OS*

	Univariate			Multivariate		
Variable	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**
Sex	0,773	0,505 - 1,182	0,236			
Age	1,353	0,885 - 2,069	0,162			
Histologic type	0,529	0,345 - 0,812	0,004	0,955	0,593 - 1,537	0,849
pT	3,423	2,024 - 5,790	**<0,0001**	1,412	0,708 - 2,817	0,326
pN	3,951	2,464 - 6,336	**<0,0001**	2,101	1,025 - 4,306	**0,043**
TNM Stage	4,685	2,887 - 7,602	**<0,0001**	1,59	0,733 - 3,448	0,24
Type of resection	1,239	0,811 - 1,895	0,321			
Combined resection	2,61	1,701 - 4,005	**<0,0001**	1,237	0,716 - 2,138	0,444
Radicality	0,128	0,074 - 0,221	**<0,0001**	0,18	0,096 - 0,337	**<0,0001**
Margin status	1,671	0,768 - 3,634	0,195			
Severe complications	2,034	1,194 - 3,465	**0,009**	2,204	1,240 - 3,918	**0,007**

OS: overall survival; HR: hazard ratio; CI: confidence interval

Discussion

Surgical resection with curative intent is still the mainstay of treatment. Postoperative morbidity results in longer hospital stays, increased costs and eventual delay in the administering of adjuvant therapy, with negative impact not only on the immediate quality of life but also on the possible decrease in survival chance

In literature there is no consensus about the definition of both complications;this datum increases the risk of non-standard evaluation of outcomes of a specific surgical procedure. In order to prevent such inconvenience, a new evaluation method, validated by a prospective cohort study examining 6.336 patients following elective surgery, was proposed in 2004 [18]. This method proved to be a valuable instrument for the qualitative assessment of a surgical treatment [19]. This system classifies as complications any deviation from standard postoperative course.

In literature morbidity rates after surgery for GC range from 25 and 46% in Western Countries and mortality rates reach a maximum of 13%. Eastern data, on the contrary, show significantly lower values. Five-year survival as well is significantly different. A survey conducted by the American College of Surgeon reports overall survival rates of 19% [20]; Japanese centres document five-year survival rates ranging over 50% with peaks reaching 70% for curative resections[21]. It's Japanese School's firm conviction that such results are linked to a more aggressive surgical approach, when compared to Western standards. We should also acknowledge both Japanese patients' different demography, being such patients younger and showing fewer comorbidities, and Japanese screening programs, resulting in high percentages of Early Gastric Cancer diagnoses.

On our study, in accordance with similar Western surveys [10,14,22,23], overall and severe morbidity rates were found to be at respectively 40,1% and 17,8%, meaning that conservatively-treated complications did represent the most relevant portion. Among these, early anastomotic stenoses were the most frequent local complications. They are generally caused by oedema and tend to regress within a 1-2 weeks' period; studies do not generally include them among the morbility calculation. The second most frequent local complication was found to be the presence of abscesses and fluid collection (9,2%) as well as anastomotic leak (6,6%). The recorded mortality rate was 5,3%.

The analysis of the collected data did not show any statistically significant connection between the evaluated variables and the global incidence of complications. Some authors found age as a risk factor [22,19], but there is no total agreement on this point. Age does not represent a contraindication for surgery, elderly patients not show a worse prognosis than younger ones [24,25].

Several studies have shown a higher mortality in elderly patients after total gastrectomy; therefore in elderly patients surgical strategy should be evaluated according to their comorbidities and tumour extent and by taking into account what quality of life the treatment can grant (26). Gastric resection implies lower complications and fewer postoperative deaths, ensuring long-term survival rates comparable to those attested after total gastrectomy.

On our study the patients undergoing total gastrectomy were on average younger than those treated with partial resection (68,4 vs 77,4). This element can reflect the

different epidemiology of tumoral histotypes, being the distally located intestinal type more frequent in elderly patients, but it can also be the result of a careful preoperative evaluation. The overall incidence of complications was higher after total gastrectomy (43,8 vs 34,3). Complications ranking either grade III or over, they turned out to be more frequent after total gastrectomy (23,2% vs 10,5%), with a statistical significance (p = 0,048). This datum reinforces the indication for a less aggressive surgery, whenever it may be possible to satifsy the aformentioned conditions. The need to perform a resection extending to adjacent organs was identified as risk factor for severe complications (p = 0,024). In literature multi-organ resection is recognized as a procedure affected by higher incidence of adverse events in the postoperative course [19,22,23] and in particular, randomized studies have reported increases in morbidity and mortality linked to splenectomy and pancreatectomy [27], those being no longer routinely performed unless in case of direct tumour invasion. The prolonged operative time resulted a risk factor for severe complications (p = 0,0196). Postoperative mortality has mainly affected male subjects (75% vs 25%), older than 75 years (75% vs 25%, mean age being 77,6), undergoing total gastrectomy (75% vs 25%), in an advanced stage of the disease (3 cases in stage III, 2 cases in stage IV) but none of these variables resulted statistical significant. The only statistically relevant correlation was the need for urgent surgery (p = 0,02).

The depth of wall invasion is one of the most important prognostic factors. The poor prognosis of patients with gastric cancer in Europe is largely due to late diagnosis.

In our study, 28,3% of patients has been classified as pT3 and 36,2% as pT4. The main cause of death in patients treated with gastrectomy for stomach cancer is recurrent disease and it occurs in most cases within the first 2 years after surgery [28,29]. The analysis of the overall survival curves of patients examined in our series supports this evidence, as most of deaths is recorded to have occurred within the first 24 months and to have affected almost half of the subjects (59% of patients with severe complications, 47% of patients without severe complications). Patients who developed severe complications showed worse (29%) five-year survival rates when compared to patients without severe complications (38%). In our series the occurrence of severe complications emerged as a prognostic factor for five-year overall survival (p = 0.007).

Despite postoperative complications' effect was reported in literature as a prognostic factor, the mechanisms beneath this connection are still an unsolved problem. The most commonly debated hypotesis considers the prolonged systemic inflammatory response established in patients undergoing complications to act as inductor for an immunosuppressive state allowing residual micrometastatic cells to migrate more rapidly and proliferate, thereby causing disease recurrence [11,30]. Jin et al. remarked that patients with complications had 50% possibilities less to be receiving adjuvant therapy [11,14]. Kubota et al. have stressed a relevant increase in white blood cells, C-reactive protein and body temperature on patients having developed complications, such evidences clearly signalling a major systemic inflammatory response [45]. Kubota's study concluded that a greater attention paid to surgical details would be the key for better prognosis. His study also evidenced that patients with postoperative complications should be followed closely over a long-term period, being more likely to develop cancer recurrence.

In conclusion, surgery still stands as the main treatment for gastric cancer and the only one able to achieve a curative therapy. When carried out within high-volume centres, with more than 20 gastrectomies per year, performed by highly skilled surgeons, it represents a safe treatment, affected by acceptable morbidity and mortality rates.

The greatest focus must be placed on the planning of the therapeutical strategy in order to minimize surgical stress, to the postoperative monitoring and to the management of postoperative complications.

The poor prognosis for these patients is mainly related to advanced stage at presentation, thus confirming the need to increase early diagnosis in order to detect larger percentages of early gastric cancer.

Riassunto

BACKGROUND: L'intervento chirurgico resettivo rimane il principale trattamento curativo per il cancro gastrico ma risulta ancora gravato da alti tassi di morbilità e mortalità postoperatorie soprattutto in Occidente.

MATERIALI E METODI: Abbiamo analizzato i pazienti trattati per cancro gastrico presso l'Unità operativa di Chirurgia generale e Trapianti d'Organo dell'Azienda Ospedaliera Universitaria di Parma dal 1/1/2006 al 31/12/2010 correlando l'insorgenza di eventuali complicanze al sesso, età, esame istologico definitivo, tipo e durata di intervento chirurgico, estensione della linfadenectomia e sopravvivenza.

RISULTATI: I casi trattati chirurgicamente sono stati 152 (media 30.4 gastrectomie/anno). 62 pazienti hanno sviluppato almeno un evento avverso nel postoperatorio per un totale di 108 eventi. Di questi 71 erano di grado I-II secondo la classificazione Clavien-Dindo, 26 di grado III. La mortalità postoperatoria ha riguardato 8 pazienti (5.3%). L'analisi dei dati non ha rilevato nessuna associazione statisticamente significativa fra le variabili considerate e l'incidenza globale di complicanze. Per le complicanze severe si sono rivelati fattori di rischio il tipo di gastrectomia, l'esecuzione di una resezione allargata e la durata prolungata dell'intervento. Il tasso di sopravvivenza globale a 5 anni è stato del 36,7%, più basso nei

pazienti con complicanze severe (29%) rispetto ai pazienti senza complicanze severe (38%). La radicalità dell'intervento, l'invasione linfonodale e lo sviluppo di complicanze severe si sono rivelati fattori prognostici significativi per la sopravvivenza globale a 5 anni.
CONCLUSIONI: la chirurgia rimane il principale trattamento per cancro gastrico e l'unico in grado di operare una terapia curativa. In centri ad alto volume (con più di 20 gastrectomie per anno) rappresenta un intervento sicuro con bassa incidenza di mortalità. Grande attenzione va posta all'accurata selezione preoperatoria, al trattamento delle comorbilità preesistenti, alla modulazione della strategia terapeutica al fine di minimizzare lo stress chirurgico, al monitoraggio postoperatorio e alla gestione delle eventuali complicanze per il possibile impatto non solo sui risultati a breve termine ma anche sulla sopravvivenza globale e libera da malattia. La prognosi infausta correlata alla presentazione in stadio già avanzato conferma la necessità di aumentare la diagnosi precoce per identificare stadi iniziali in percentuali più elevate.

References

1. Forman D, Burley VJ: *Gastric cancer: Global pattern of the disease and an overview of environmental risk factors*. Best Pract Res Clin Gastroenterol, 2006; 20:633-49.

2. Del Rio P, et al.: *Advanced stage gastric cancer and neoadjuvant chemotherapy. Our experience in surgical resectability*. Ann Ital Chir, 2013; 84.(6):623-29.

3. Washington K: *7th edition of the AJCC cancer taging manual: stomach*. Ann Surg Oncol, 2010; 17(12):3077-79.

4. Greene FL, Page DL, Fleming ID, Fritz A, Balch CM, Haller DG, Morrow M (eds): *American Joint Committee on Cancer: AJCC Cancer Staging Manual*, 6th ed. New York: Springer, 2002.

5. Sianesi M, Bezer L, Del Rio P, et al.: *The Node Ratio as a prognostic factor after curative resection for gastric cancer*. Journal of Gastrointestinal Surgery, 2010; 14:614-19.

6. Paoletti X, Oba K, Burzykowski T, Michiels S, Ohashi Y, Pignon JP, Rougier P, Sakamoto J, Sargent D, Sasako M, et al.: *Benefit of adjuvant chemotherapy for resectable gastric cancer meta-analysis*. JAMA. 2010; 303:1729-737.

7. Kelsen DP: *Adjuvant and neoadjuvant therapy for gastric cancer*. Semin Oncol, 1996; 23(3):379-89.

8. Cunningham D, Allum WH, Stenning SP, Thompson JN, van de Velde CJ, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S, Chua YJ, MAGIC Trial Participants: *Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer*. N Engl J Med 2006; 355(1):11-20.

9. Zi-Yu Li, Fei Shan, Lian-Hai Zhang, Zhao-De Bu, Ai-Wen Wu, Xiao-Jiang Wu, Xiang-Long Zong, Qi Wu, Hui Ren, Jia-Fu JI: *Complications after radical gastrectomy following FOLFOX7 neoadjuvant chemotherapy for gastric cancer*. World J Surg Oncol, 2011; 9:110.

10. Badgwell B, Ajani J, Blum M, Ho L, Fournier K, Chiang YJ, matamoros a, das p, mansfield p: *postoperative morbidity and mortality rates are not increased for patients with gastric and gastroesophageal cancer who undergo preoperative chemoradiation therapy*. Ann Surg Oncol, 2015.

11. Papenfuss WA, Kukar M, Oxenberg J, Attwood K, Nurkin S, Malhotra U, Wilkinson NW: *Morbidity and mortality associated with gastrectomy for gastric cancer*. Ann Surg Oncol, 2014; 21(9):3008-14.

12. Lee KG, Lee HJ, Yang JY, Oh SY, Bard S, Suh YS, Kong SH, Yang HK: *Risk factors associated with complication following gastrectomy for gastric cancer: Retrospective analysis of prospectively collected data based on the Clavien-Dindo system*. J Gastrointest Surg, 2014; 18(7):1269-277.

13. Jeong O, Kyu Park Y, Ran Jung M, Yeop Ryu S: *Analysis of 30-day postdischarge morbidity and readmission after radical gastrectomy for gastric carcinoma: A single-center study of 2107 patients with prospective data*. Medicine (Baltimore), 2015; 94(11):e259.

14. Linda LX. Jin L, Sanford, DE ,Hart Squires M III, Lindsey EM, Yan Yan, Poultsides GA, Konstantinos I. Votanopoulos, Sharon M. Weber, Mark Bloomston, Timothy Pawlik M, Hawkins WG, Linehan DC, Schmidt C, Worhunsky DJ, Acher AW, Cardona K, Cho CS, Kooby DA, Levine EA, Winslow E, Saunders, Gaya Spolverato N, Colditz GA, Maithel SK, Fields RC: *Interaction of postoperative morbidity and receipt of adjuvant therapy on long-term survival after resection for gastric adenocarcinoma: Results from the u.s. gastric cancer collaborative*. Ann Surg Oncol, 2016.

15. Yoo HM, Lee HH, Shim JH, Jeon HM, Park CH, Song KY: *Negative impact of leakage on survival of patients undergoing curative resection for advanced gastric cancer*. J Surg Oncol, 2011; 104(7):734-40.

16. Sierzega M, Kolodziejczyk P, Kulig J: Polish Gastric Cancer Study Group: *Impact of anastomotic leakage on long-term survival after total gastrectomy for carcinoma of the stomach*. Br J Surg, 2010; 97(7):1035-42.

17. Qing-Guo Li, Ping Li, Dong Tang, Jie Chen, Dao-Rong Wang: *Impact of postoperative complications on long-term survival after radical resection for gastric cancer*. World J Gastroenterol, 2013; 19(25): 4060-65.

18. Dindo D, Demartines N, Clavien PA: *Classification of surgical complications a new proposal with evaluation in a cohort of 6336 patients and results of a survey*. Ann Surg, 2004; 240(2):205-13.

19. Junfeng Zhou, Peiwu Yu, Yan Shi, Bo Tang, Yingxue Hao, Yongliang Zhao, Feng Qian: *Evaluation of Clavien-Dindo classification in patients undergoing total gastrectomy for gastric cancer*. Med Oncol, 2015; 32:120.

20. Wanebo HJ, Kennedy BJ, Chmiel J, Steele G Jr, Winchester D, Osteen R: *Cancer of the stomach. A patient care study by the American College of Surgeons*. Ann Surg, 1993; 218(5):583-92.

21. Doglietto GB, Rosa F, Bossola M, Pacelli F: *Lymphadenectomy for gastric cancer: Still a matter of debate?* Ann Ital Chir, 2012; 83(3):199-207.

22. Bartlett EK, Roses RE, Kelz RR, Drebin JA, Fraker DL, Karakousis GC: *Morbidity and mortality after total gastrectomy for gastric malignancy using the American College of Surgeons National Surgical Quality Improvement Program database*. Surgery, 2014; 156(2):298-304.

23. Viste A, Haùgstvedt T, Eide GE, Søreide O: *Postoperative complications and mortality after surgery for gastric cancer*. Ann Surg, 1988; 207(1):7-13.

24. Pisanu A, Montisci A, Piu S, Uccheddu A: *Curative surgery for gastric cancer in the elderly: Treatment decisions, surgical morbidity, mortality, prognosis and quality of life.* Tumori, 2007; 93(5):478-84.

25. Gretschel S, Estevez-Schwarz L, Hünerbein M, Schneider U, Schlag PM: *Gastric cancer surgery in elderly patients.* World J Surg, 2006; 30(8):1468-74.

26. Roviello F, Marrelli D, De Stefano A, Messano A, Pinto E, Carli A: *Complications after surgery for gastric cancer in patients aged 80 years and over.* Jpn J Clin Oncol, 1998; 28(2):116-22.

27. Degiuli M, Sasako M, Calgaro M, Garino M, Rebecchi F, Mineccia M, Scaglione D, Andreone D, Ponti A, Calvo F: Italian Gastric Cancer Study Group: *Morbidity and mortality after D1 and D2 gastrectomy for cancer: interim analysis of the Italian Gastric Cancer Study Group (IGCSG) randomised surgical trial.* Eur J Surg Oncol, 2004; 30(3):303-08.

28. Marrelli D, De Stefano A, de Manzoni G, Morgagni P, Di Leo A, Roviello F: *Prediction of recurrence after radical surgery for gastric cancer: A scoring system obtained from a prospective multicenter study*. Ann Surg, 2005; 241(2):247-55.

29. Verlato G, Marrelli M, Accordini S, Bencivenga M, Di Leo A, Marchet A, Petrioli R, Zoppini G, Muggeo M, Roviello F, de Manzoni G: *Short-term and long-term risk factors in gastric cancer.* World J Gastroenterol, 2015; 21(21): 6434-443.

30. Kong F, Qi Y, Liu H, Gao F, Yang P, Li Y, Jia Y: *Surgery combined with chemotherapy for recurrent gastric cancer achieves better long-term prognosis*. Clin Transl Oncol, 2015.