

European single-center experience on 356 operated patients for gastric cancer



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AIM: Surgery in association with lymphadenectomy is the treatment of choice for the gastric adenocarcinoma. Aim is to report our experience in the surgical treatment of gastric cancer in a European center.

MATERIAL AND METHODS: A prospectively maintained database identified 515 patients. Staging laparoscopy was performed to rule out peritoneal carcinomatosis in suspicious cases. Type of surgery and lymphadenectomy were determined according to the Japanese guidelines and pathological staging according to the TNM classification. Survival was analyzed using the Kaplan-Meier method.

RESULTS: Staging laparoscopy avoided 150 (29.1%) unnecessary laparotomies. A total of 356 patients underwent surgery with curative intent. Overall postoperative morbidity and mortality rates were 16.8% and 5.9%, respectively. Two hundred-fifty-one patients (70%) were T3-T4. Negative lymph-nodes were observed in 71 patients (19.9%). One-hundred-seventy-nine were at least stage III. At a mean follow-up of 80.6 months, the overall and disease-free survival rates were 54.4% and 50.6%, respectively. The survival stratification based on the type of lymphadenectomy showed an overall survival rate of 43% and 65.5% in case of D1 and D2 lymphadenectomy, respectively. Based on the tumor stage the overall survival rate was 90%, 62.7%, 36.4% and the disease-free survival was 90%, 54.3%, 31.3%, for stage I, II and III, respectively.

CONCLUSIONS: Total or subtotal gastrectomy with D2 lymphadenectomy and adjuvant therapy for the treatment of locally advanced gastric cancer proved a valuable strategy. Staging laparoscopy is recommended.

KEY WORDS: Gastric cancer, Laparoscopy, Lymphadenectomy, Prognosis, Surgery

Introduction

Approximately 951.000 new cases of gastric cancer were diagnosed in the world in 2012, representing 6.8% of all malignant neoplasms and the fifth tumor for incidence after lung, breast, colorectal and prostate cancers¹. Gastric carcinoma is the third leading cause of death in the

world due to cancer, with 723.000 deaths per year (8.8% of the total deaths for neoplasms). More than 70% (677.000) of cases occur in developing countries and about half of total number in Eastern Asia¹.

Despite a significant reduction of incidence in most industrialized countries, the 5-year survival rate of gastric cancer does not currently exceed 20-30%². Only 15-20% of patients show limited disease at diagnosis while 65% present loco-regional or distant dissemination³. Beyond endoscopy with biopsies and Computed Tomography (CT) scan, endoscopic ultrasound and staging laparoscopy can be useful diagnostic tools in many cases⁴.

Surgery associated with an extensive lymphadenectomy is considered the curative treatment of choice^{4,5}. In case

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of locally advanced gastric cancer (T3-T4 or N+), the use of neoadjuvant chemotherapy showed promising results ^{6,7}.

The aim of the present study is to report our experience in the surgical treatment of gastric cancer in a European reference center.

Materials and Methods

A prospectively maintained database identified 515 patients with diagnosis of gastric carcinoma operated in our department between October 1998 and October 2016. Institutional review board approval and informed consent from all participants included in the study were obtained. The medical records were reviewed for age, gender, tumor location, stage, type of surgery, postoperative morbidity, mortality, survival rate and mortality at follow up.

Preoperative work-up included preoperative endoscopy with biopsies and staging with CT scan and endoscopic ultrasonography in all patients ⁸.

A preliminary staging laparoscopy was performed in 201 cases with suspicious of peritoneal carcinomatosis and after that 150 patients (74.6%) were excluded from radical surgical treatment and 9 underwent cytoreductive surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC). Finally, a total 356 patients underwent surgery with curative intent were included in the present study.

The choice of operation and lymphadenectomy was based on the Japanese guidelines ⁹. Splenectomy was performed in presence of metastatic bulky hilum lymph-nodes or direct organ infiltration. When gastric tumor involved other organs, an extended resection was performed ¹⁰.

The reconstruction type was mechanical Roux-en-Y esophago-jejunal anastomosis after total gastrectomy, performed with circular stapler in all cases. Gastro-jejunostomy or gastro-duodenostomy after subtotal resection were also mechanically performed.

Tumor grading and staging was defined according to the last TNM gastric cancer classification ¹¹. Overall morbidity included medical and surgical complications ¹². Postoperative mortality included all deaths occurring during hospitalization.

Patients with II-III stage gastric cancer underwent adjuvant chemotherapy with folinic acid, fluorouracil and irinotecan.

Follow up information was regularly obtained from outpatient clinical visits from the time of surgery to December 2016, according to a previously described protocol ¹³. If a patient was still alive at the time of the last visit, survival was censored.

STATISTICAL ANALYSIS

Statistical analysis was performed using the Fisher's exact test. A probability (p) value lower than 0.05 was consi-

dered statistically significant. Overall survival (OS) curves were calculated by the Kaplan-Meier product limit method from the date of surgery until disease progression or death. Statistical analysis was carried out with SPSS software 22.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

One hundred-ninety-four man (54.5%) and 162 women (45.5%) were included in the study (mean age 69 years, range 29-91). Table I shows tumor location and the type of surgery performed.

One hundred-two postoperative surgical complications occurred in 60 patients (16.8%). Overall incidence of anastomotic leakage was 10.7%. Table 2 shows complications based on the type of surgery and extension of lymphadenectomy performed.

The overall 30-day postoperative mortality rate was 5.9% (21 patients). Sixteen patients (76.2%) died for surgical complications (11 anastomotic leakages, 3 bleeding, 2 acute pancreatitis) while 5 patients (23.8%) died for medical complications (3 myocardial infarctions, 2 respiratory failures). Mean postoperative hospital stay was 19 days (range 9 - 90 days).

Two hundred-fifty-one patients (70.5%) were staged T3-T4. The mean number of resected lymph-nodes was 28.3 (range 2 - 114). Negative lymph-nodes were observed in 71 patients (19.9%). One hundred-seventy-nine patients (50.2%) were stage III or more. Undifferentiated tumors (G3) represented 64.9% of patients (231).

TABLE I - Tumor location and type of surgery.

Tumor location	n (%)
Cardias	65 (18.2)
Fundus	26 (7.3)
Body	113 (31.7)
Antrum	134 (37.6)
Gastric stump	13 (3.7)
Multifocal	5 (1.4)
Type of surgery, n (%)	
Total gastrectomy	171 (48)
Subtotal gastrectomy	185 (52)
Lymphadenectomy, n (%)	
D1	73 (20.5)
D2	247 (69.4)
D3	36 (10.1)
Other resection, n (%)	
Splenectomy	61 (17.1)
Pancreatectomy	5 (1.4)
Transverse colon resection	12 (3.4)
Liver resection	8 (2.2)
Left adrenalectomy	6 (1.7)

HIPEC: Hyperthermic Intraperitoneal Chemotherapy

TABLE II - Complications based on the type of surgery and lymphadenectomy performed.

	Type of surgery		Total N = 356	Type of lymphadenectomy			Total N = 356
	Subtotal gastrectomy n = 185	Total gastrectomy n = 171		D1 n = 73	D2 n = 247	D3 n = 36	
Bleeding, n (%)	16 (8.6)	10 (5.8)	26 (7.3)	6 (8.2)	20 (8)	0	26 (7.3)
Leakage, n (%)	15 (8.1)	23 (13.4)	38 (10.7)	8 (10.9)	23 (9.3)	7 (19.4)	38 (10.7)
Pancreatitis, n (%)	8 (4.3)	9 (5.2)	17 (4.8)	0	14 (5.6)	3 (8.3)	17 (4.8)
Lymphorrea, n (%)	1 (0.5)	7 (4)	8 (2.2)	0	6 (2.4)	2 (5.5)	8 (2.2)
Abscess, n (%)	4 (2.1)	9 (5.2)	13 (3.6)	1 (1.3)	9 (3.6)	3 (8.3)	13 (3.6)
Total, n (%)	44 (23.7)	58 (33.9)		15 (20.5)	72 (29.1)	15 (41.6)	
p value	0.0458 *			D1 vs D2: 0.1781 D1 vs D3: 0.0059* D2 vs D3: 0.1747			

Vs: versus. *: statistically significant differences in bold.

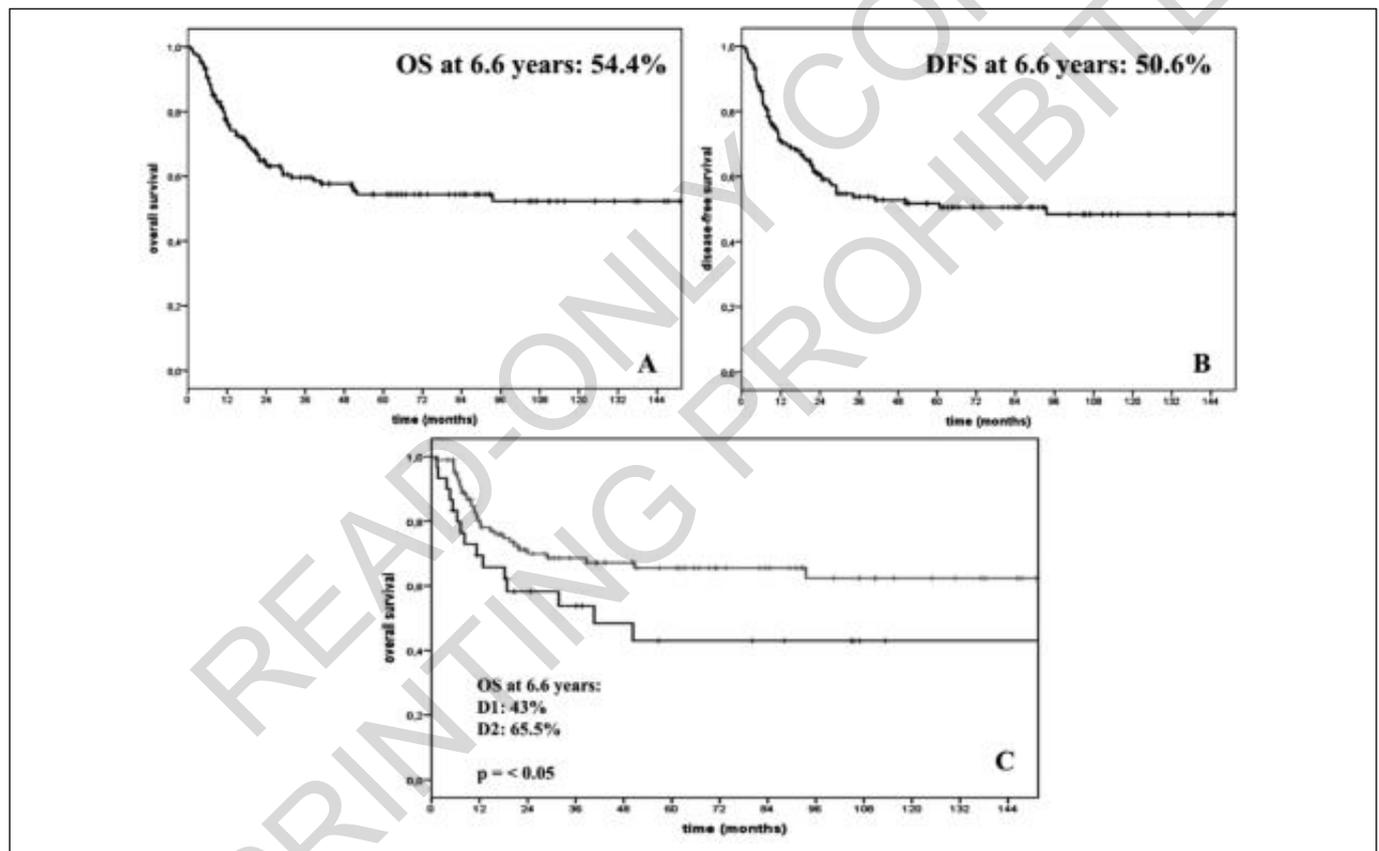


Fig. 1: Overall survival (OS) (A). Disease-free survival (DFS) (B) at 6.6 years. Overall survival (OS) at 6.6 years based on the type of lymphadenectomy (C).

At a mean follow up of 80.6 months (range 2- 180 months) 128 patients (36%) were dead. Of these, 31 patients underwent D1, 62 D2 and 35 D3 lymphadenectomy (24.2%, 48.5% and 27.3%, respectively). Tumor progression was observed in 94 patients (28%) as follows: peritoneal carcinomatosis n = 27 patients (28.7%), distant metastases n = 12 patients (12.7%), local recurrence n = 21 patients (22.3%) and not specified progression n = 34 patients (36.1%).

According to the actuarial method of Kaplan-Meier, the overall survival rate at 6.6 years (80.6 months) was 54.4% and the disease-free survival rate was 50.6% (Fig. 1 A-B). The survival stratification based on the type of lymphadenectomy showed an overall survival rate of 43% and 65.5% (p = <0.05) in case of D1 and D2 lymphadenectomy, respectively (Fig. 1 C). Based on the tumor stage the overall survival rate was 90% stage I, 62.7% stage II, 36.4% stage III and the disease-free survival

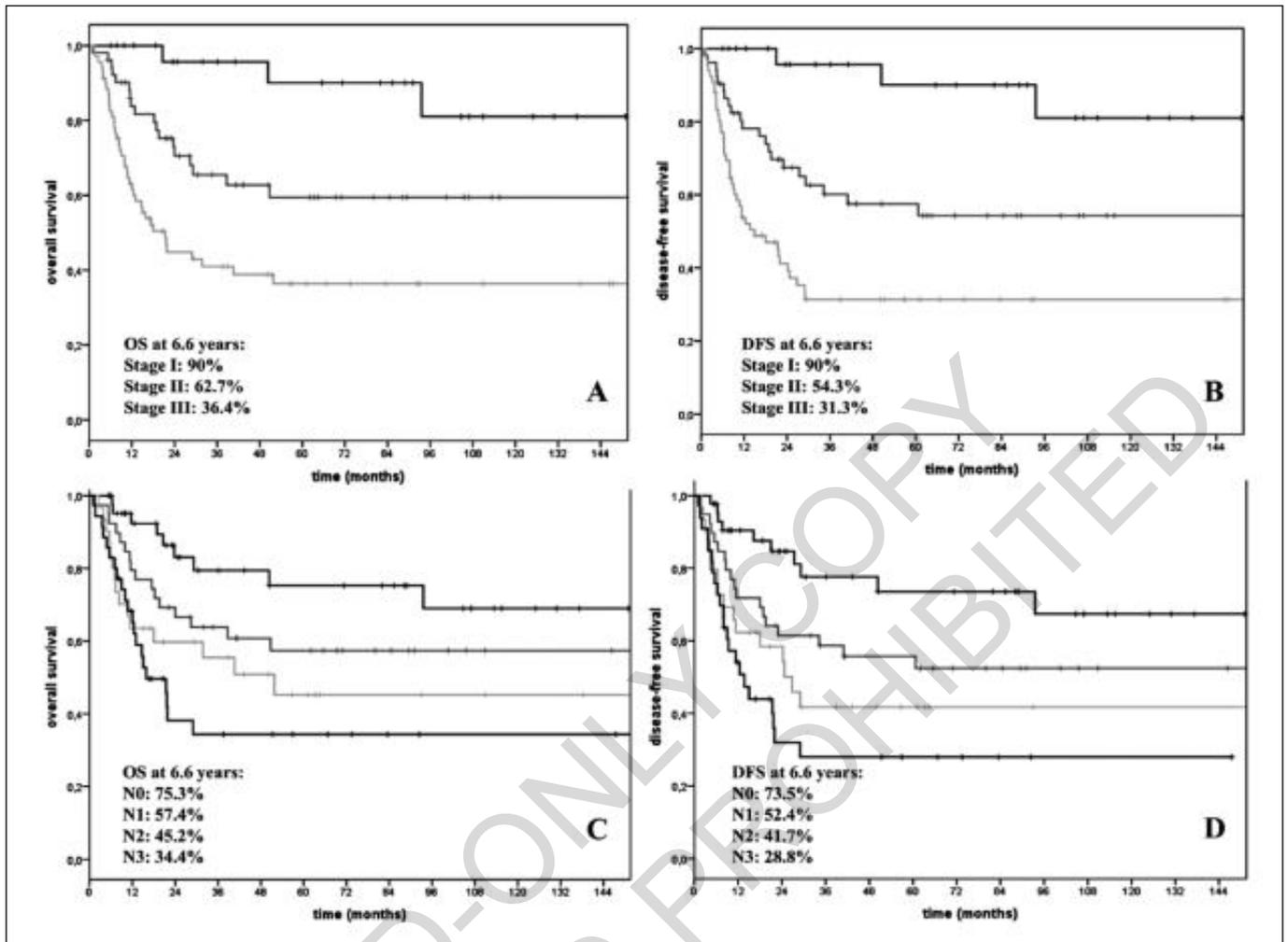


Fig. 2: Overall survival (OS) (A) and disease-free survival (DFS) (B) at 6.6 years based on the tumor stage. OS (C) and DFS) (D) at 6.6 years based on the N stage.

was 90% stage I, 54.3% stage II, 31.3% stage III (Fig. 2 A-B). Based on the N stage, the overall survival rate was 75.3% N0, 57.4% N1, 45.2% N2 and 34.4% N3 and the disease-free survival rate was 73.5% N0, 52.4% N1, 41.7% N2 and 28.8% N3 (Fig. 2 C-D).

Discussion

We analyzed our experience in the surgical treatment of gastric cancer. In a series of 356 patients the postoperative morbidity and mortality rates were 16.8% and 5.9%, respectively. After a mean follow up of 80.6 months, the overall survival and the disease-free survival rates were 54.4% and 50.6%, respectively.

One of the major problems of gastric cancer is related to the delayed diagnosis and consequently the peritoneal involvement at this time⁶. In case of distant metastases or peritoneal carcinomatosis, CT scan has a sensitivity of 74% and 33%, respectively, while the specificity

reported is 99% in both cases¹⁴. Endoscopic ultrasound allows to achieve a good definition of the tumor invasion depth, showing a sensitivity and specificity to discriminate T1-T2 from T3-T4 cancer of the 86% and 90%, respectively, while in the nodal staging showed a sensitivity and specificity of 83% and 67%, respectively¹⁵. Positron Emission Tomography (PET) / CT scan may be helpful to detect the peritoneal involvement, but it has several limitations due to the histologic subtypes and the spatial resolution that do not allow to correctly establish the patients' therapeutic program¹⁶.

On the other hand, laparoscopy provides a direct and magnified view of the peritoneal cavity and during this procedure is possible to perform biopsy or intraoperative ultrasound in order to diagnose peritoneal carcinomatosis or liver metastases, resulting in a change of treatment strategy in up to 51% of cases¹⁷. In the present series, 201 staging laparoscopies were performed, avoiding unnecessary explorative laparotomies in approximately one third of cases. For these reasons, we consider

staging laparoscopy mandatory in these patients. This diagnostic approach is useful especially in locally advanced tumors, according to the 2012 consensus conference of the European Organization for research and treatment of Cancer (EORTC) ¹⁸.

A major topic of gastric surgery is the extension of lymphadenectomy. In a recent meta-analysis with 1599 patients, El-Sedfy et al. showed no statistical differences in the survival rates between D1 (44.8%) and D2 (47%) lymphadenectomy at 5 years follow up ¹⁹. However, in a subgroup analysis, a significant survival difference in case of T3 patients who underwent D2 lymphadenectomy, was evident (D2 25.9% versus D1 11.5%) ¹⁹. Songun et al. demonstrated a higher survival rate in case of D2 lymphadenectomy (48%) in comparison to D1 lymphadenectomy (37%) after 15 years ²⁰. These data are confirmed in the present series in which the overall survival rate was 65.5% in case of D2 lymphadenectomy in comparison to 43% in case of D1 ($p = <0.05$), confirming that a more aggressive approach is associated with significant advantage in terms of survival benefit. The overall survival rate of N3 patients in this series was 34.4%, providing a good result if compared to the literature ²¹. In these patients, the extended lymphadenectomy provides significant benefit, especially if associated with chemotherapy.

The overall postoperative morbidity rate was 16.8%, with a statistically significant difference in the incidence of postoperative complications based on lymphadenectomy only between D1 and D3. Even if, the highest incidence rate of reoperation reported in the literature is observed in case of D2 lymphadenectomy (11.4%) ²². This discrepancy in the present series could be related to the exiguous number of patients who underwent D3 lymphadenectomy.

Concerning the difference in postoperative mortality rates between D2 and D1 lymphadenectomy, even though a recent meta-analysis showed higher mortality rate for D2 in early series (10.5% versus 4.6%), in our experience this difference was not observed ²³. In the present study, the overall mortality rate was 5.9% but the sample of patients is composed for the half of cases of at least stage III tumor, 80% of cases N+ and at least T3 tumor in about 90% of patients.

The incidence rate of splenectomies or distal spleno-pancreatectomies was 18.5% in this series, mostly occurring at the beginning of our experience. If not indicated, splenectomy should be avoided due to the increase of postoperative morbidity without survival improvement ²³.

Tumor progression is another important topic for these patients. Recurrences are related to several factors, such as tumor stage and extension of surgery, occurring mostly within the first two years after surgery ²⁴. In the present series they were observed in 94 patients (28%), with a maximum incidence (50%) in the first 24 months. Peritoneum represented the most common site of recurrences (28.7%), as reported in literature ²³. These data point out the need for a multidisciplinary approach and

currently HIPEC seems to be a good option, especially if used in adjuvant setting for the prevention of peritoneal carcinomatosis ²⁵. Since peritoneal recurrences represent the principal challenge for patients with subserosa and serosa infiltration, in our opinion, combining cytoreductive surgery with HIPEC could be an effective treatment in these cases ²⁵.

Several treatment strategies have been proposed for gastric cancer. If surgery is the treatment of choice for resectable cancers, there is still no consensus on which therapy should be associated in locally advanced lesions ²⁵. Perioperative chemotherapy is recommended in Northern Europe, adjuvant chemo-radiotherapy or perioperative chemotherapy in North America and adjuvant chemotherapy in Japan ²⁶⁻²⁸. The increasing identification of new prognostic biologic factors such as E-cadherin, Epidermal Growth Factor Receptor (EGFR), DNA mismatch repair, satellite micro instability, variations in expression of several factors including thymidylate synthase, beta-catenins, anti-mucin antigen, p53, COX-2, matrix metalloproteases, vascular endothelial growth factor receptor ²⁹⁻³¹ may represent novel targets. A recently published paper from our work group showed that modulation of aberrant expression of miR-204, which in turn releases oncogenic Bcl-2 protein activity, might hold promise for preventive and therapeutic strategies of gastric cancer ³².

This study has some limitations. The analysis was non-randomized, and it is retrospective. A relatively small sample size covering a long period was enrolled but it includes 356 consecutively operated patients coming from a single-center Western country.

Conclusions

The diagnostic strategy should improve patients' selection for neoadjuvant therapies and staging laparoscopy appears mandatory in case of suspected peritoneal carcinomatosis. Total or subtotal radical gastrectomy with D2 lymphadenectomy and adjuvant therapy in case of T3-T4 or N+ lesions proved a valuable strategy of treatment. A multidisciplinary approach is necessary for the treatment of locally advanced gastric carcinoma, considering that it remains a severe disease with high mortality risk.

Riassunto

OBIETTIVO: La chirurgia associata alla linfadenectomia è il trattamento di scelta per l'adenocarcinoma gastrico. Lo scopo del presente studio è quello di riportare la nostra esperienza nel trattamento chirurgico del cancro gastrico in un centro europeo.

MATERIALI E METODI: Da una base di dati prospettica sono stati identificati 515 pazienti. La laparoscopia di

stadiazione è stata eseguita per escludere la carcinosi peritoneale in casi sospetti. Il tipo di intervento chirurgico e la linfadenectomia sono stati determinati in base alle linee guida giapponesi e alla stadiazione patologica secondo la classificazione TNM. La sopravvivenza è stata analizzata utilizzando il metodo Kaplan-Meier.

RISULTATI: La laparoscopia di stadiazione ha evitato 150 (29.1%) leparotomie non necessarie. Un totale di 356 pazienti sono stati sottoposti a intervento chirurgico con intento curativo. Complessivamente i tassi di morbilità e mortalità postoperatoria erano del 16.8% e del 5.9%, rispettivamente. Duecentocinquanta pazienti (70%) erano T3-T4. Linfonodi negativi sono stati osservati in 71 pazienti (19.9%). Cento-settantatré erano almeno in stadio III. Ad un follow-up medio di 80.6 mesi, i tassi di sopravvivenza globale e libera da malattia erano rispettivamente del 54.4% e del 50.6%. La stratificazione di sopravvivenza basata sul tipo di linfadenectomia ha mostrato un tasso di sopravvivenza globale del 43% e del 65.5% in caso di linfadenectomia D1 e D2, rispettivamente. In base allo stadio del tumore, il tasso di sopravvivenza globale era del 90%, 62.7%, 36.4% e la sopravvivenza libera da malattia era del 90%, 54.3%, 31.3%, rispettivamente per gli stadi I, II e III.

CONCLUSIONI: La gastrectomia totale o subtotale con linfadenectomia D2 e terapia adiuvante per il trattamento del carcinoma gastrico localmente avanzato si è dimostrata una strategia valida. La laparoscopia di stadiazione è raccomandata.

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