Experience of 463 cases of gastric cancer from a single surgical center

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AIM: *To evaluate clinical and histopathological changes of gastric cancer (GC) in the last fifteen years and analyze factors influencing overall survival.*
MATERIAL OF STUDY: *We have retrospectively categorized patients submitted to surgery for GC from January 1996 to December 2010. The analysis focused on two periods: 1996-2003 (period 1) and 2004-2010 (period 2).*
RESULTS: *There was an increase in age distribution of GC in period 2 (p=0.012). Significant increase of whole GC was observed in period 2 (p=0.01). Slight but significant changes in TNM stage were found: in group 2 there was a decrease in the rate of early GC and in advanced depth of tumor invasion; increase of lymph nodes involvement was also demonstrated. Overall survival (OS) had not changed from the first to the second period. There was a significant difference in OS calculated for Lauren histotype: from ten months to surgery, patients with diffuse histotype showed worse prognosis.*
DISCUSSION: *The most important findings were an increase in lymph node involvement and a decrease in depth of tumor invasion, an higher percentage of whole type and a decrease in palliative surgery. Overall-survival hasn't change in the last fifteen years. These results confirms the importance of extent of lymph node dissection in the standard surgical approach of GC, the tumor stage and Lauren histotypes as the main prognostic factors in GC.*
CONCLUSION: *This work confirms the dismal prognosis of GC and the need to increase diagnosis of early gastric cancer.*

KEY WORDS: Gastric cancer, Lauren histotype, Overall survivall

Introduction

Despite a major decline in incidence and mortality, gastric cancer (GC) is still detected in around one million people every year for over 700000 deaths, representing 8% of all cancer cases and 9.7% of all cancer death [1,2]. GC is the fourth most commonly occurring carcinoma after cancer of the lung, breast and colorectum and the second most common cancer-related cause of death after lung cancer. The incidence is about twice as high in men (n= 640,031 in 2008) than in women (n=348,571 in 2008); the geographic pattern between men and women is similar. Gastric cancer occurs approximately at the same age in men (median age at diagnosis is 66 years) but at older ages in women (median age at diagnosis is 68 years)[3-6]. The prognosis of GC differs notably according to geographical area. Survival rates reported in Japanese and Korean studies are clearly higher than those in Western series, as a result of an earlier diagnosis and a more extensive surgical approach [7-11].

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The aim of this study was to evaluate clinical and histopathological changes of GC in the last fifteen years and analyse factors influencing overall-survival.

Material and Methods

We established a dedicated retrospective database to evaluate clinical and histopathological changes of GC in the last fifteen year and to analyse factors influencing overall survival. We retrospectively categorized 446 patients submitted to surgery for GC at OU General Surgery and Organ Transplantation, University Hospital of Parma, from January 1996 to December 2010.

The following data were recorded: sex, patient age, tumor location, type of surgery, urgency or election surgery, tumor size, Lauren histotype, AJCC 7th Edition TNM stage, number of lymph nodes removed (NRLN) and number of metastatic lymph nodes (NMLN), 30-days mortality. Tumor location was classified as upper, middle and lower third; when GC was involving more than two portions it was classified as whole. The main purpose of surgery was the complete resection of the tumor. The indication for performing total or sub-total gastrectomy was based on tumor localization and macroscopic appearance of the GC. For tumor located in the middle and lower thirds of the stomach a sub-total gastrectomy was generally preferred; for whole gastric cancer and for tumor of upper third of the stomach total gastrectomy was performed. Patients with unresecable locally advanced cancer were treated with palliative care (by-pass or jejunostomy); in few cases exploratory laparotomy alone was performed.

Histological type was classified according to Lauren's classification in three different type: intestinal, diffuse and mixed (due to the presence of intestinal and diffuse aspects) [12].

The last version of TNM classification of American Joint Commitee on Cancer (AJCC) was used for pathological classification and definition of residual tumor; patients with microscopical residual tumor were classified as R1 and patients without residual tumor as R0 [13-15].

Post-operative mortality was defined as death occurring within 30 days of operation.

Details of neoadjuvant and adjuvant chemotherapy were not considered in this study because the decision to treat patients with chemotherapy was made by medical oncologists who didn't participate to our study.

The analysis focused on two periods because we want to evaluate changes of GC: 1996-2003 (period 1; 220 patients) and 2004-2010 (period 2; 243 patients).

Survival status was collected through the Parma's Register of Tumors and some data were recorded by contacting the patients directly; follow up was closed in October 2014.

Patients with missing data were excluded. The Chi-square test was used for comparison of qualitative data. The normality of distribution of numerical variables was performed by means of the Kolmogorov-Smirnov test. If not normally distributed the data were compared by means of the non parametric Kruskal-Wallis test. Survival curves were estimated using the Kaplan – Meier method and compared by the log-rank test. $P < 0.05$ was considered statistically significant. Statistical analysis was performed using the Statistical Product and Service Solution,SPSS version 17.0 (SPSS, Inc., Chicago, IL, USA).

Results

Clinical pathological features

Between 1996 and 2010, 463 patients received surgical treatment for GC at OU General Surgery and Organ Transplantation, University Hospital of Parma. 416

TABLE I - *Clinical and pathological characteristics of the 463 patients analysed according to two periods.*

	All patients	Period 1	Period 2	*p* value
Sex				
man	276 (59.6%)	126 (57.3%)	150 (61.7%)	*P ns*
Woman	187 (40.4%)	94 (42.7%)	93 (38.3%)	*P ns*
Age				
Mean age	72.1	70.2	73.1	*P = 0.012*
Range	33-92 years	33-92 years	43-92 years	
Tumor Location				
Upper	50 (10.8%)	29 (13.2%)	21 (8.6%)	*P ns*
Middle	97 (20.9%)	53 (24.1%)	44 (18.1%)	*P ns*
Lower	200 (43.2%)	96 (43.6%)	104 (42.8%)	*P ns*
Whole	93 (20.1%)	34 (15.5%)	59 (24.3%)	*P = 0.01*
Gastric stump	23 (5%)	8 (3.6%)	15 (6.2%)	*p = 0.01*
Lauren Histotype				
Intestinal	220 (47.5%)	99 (45%)	121 (49.8%)	*P ns*
Diffuse	140 (30.2%)	60 (27.3%)	80 (32.9%)	*P ns*
Mixed	33 (7.1%)	11 (5%)	22 (9%)	*P ns*
Unclassified	70 (15.2%)	50 (22.7%)	20 *(8.2%)*	*p < 0.05*
Depth Of Invasion				
pT1	72 (15.5%)	37 (25.9%)	35 (14.4%)	*P ns*
pT2	39 (8.4%)	11 (5%)	28 (11.5%)	*P ns*
pT3	52 (11.2%)	2 (0.9%)	50 (20.6%)	*P ns*
pT4a	188 (40.6%)	103 (46.8%)	85 (35%)	*P ns*
pT4b	43 (9.3%)	26 (11.8)	17 (7%)	*P ns*
Limph Node Involvement				
N0	125 (27%)	61 (27.7%)	64 (26.3%)	*P ns*
N1	53 (11.4%)	18 (8.2%)	35 (14.4%)	*P ns*
N2	63 (13.6%)	38 (17.3%)	25 (10.3%)	*P ns*
N3a	83 (17.9%)	35 (15.9%)	48(19.7%)	*P ns*
N3b	62 (13.4%)	22 (10%)	40 (16.5%)	*P ns*

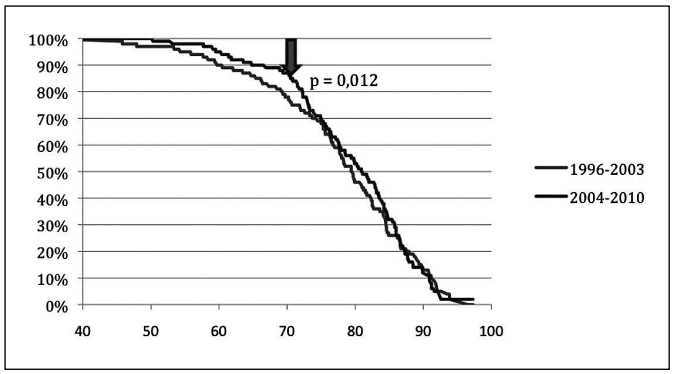

Fig. 1: *Mortality curves stratified by age of diagnosis for two periods analysed.*

patients underwent R0 or R1 surgical resection and 47 patients palliative surgery. In the Table I characteristics of the 463 patients analysed were showed and two periods two periods were compared. There was an increase in age of diagnosis - distribution of GC in period 2 (p = 0.012) like showed by mortality curves (Fig. 1); mean age in period 1 was 70,2 years (range 33 – 92 years) and in period 2 was 73,1 (range 43 – 92 years). Mean age of patients treated with elective surgery was lower than patients underwent urgency surgery. There was a significant increase in the rate of whole GC and of gastric stump in period 2 (p = 0,01); no significant differences were demonstrated in the location of GC between upper, middle and lower third of stomach.

Histopathological Factors

There wasn't any significant change in Lauren histotypes; in period 2 there was a significant decrease of unclassified type (p < 0.05); the high percentage of unclassified tumors in period 1 is probably due to not well performed histopathological analysis. Little changes in pTNM stages were demonstrated: there was a decrease in the pT4a – pT4b subgroup and an increase in pT2, pT3 and pN3a – pN3b in period 2.

Surgical Treatment

In this study 189 patients in period 1 and 227 in period 2 underwent curative surgery for GC; there wasn't any change in total gastrectomy and sub-total gastrectomy between two period. Significant decrease in palliative surgery was established in period 2 (p = 0.0001): palliative surgery in period 1 was performed in 31 patients and in 17 patients in period 2.
The number of lymph nodes removed increased with time and in period 2 there was also an increase in number of metastatic lymph nodes but without statistical significance (Table II). There was an inverted relationship between age and number of removed lymph nodes.

Table II - *Comparison of number of removed lymph nodes (NRLN) and number of metastatic lymph nodes (NMLN) between period 1 and 2.*

	All patients	Period 1	Period 2
NRLN	7761	3374	4387
mean	20,1 +/- 12,1	19,4 +/- 12,3	20,7 +/- 11,9
NMLN	2779	1148	1631
mean	7,2 +/- 9,5	6,6 +/- 9,2	7,7 +/- 9,7

Survival data

The mean overall-survival in patients with GC was 44 months. The five-years overall-survival rate was 33 % and ten-years overall-survival rate was 25 %; there weren't any significant changes between the two period. Overall survival decreased significantly over time in pN2 – N3 disease in period 1 and in period 2 (p < 0.05) (Fig. 2). Overall-survival curves stratified by Lauren histotype showed that survival probability decreased significantly over time in diffuse/mixed type (p < 0,05) (Fig. 3). There weren't any differences between two histotypes in the first ten months. Overall-survival rates were 45 % for diffuse type and 58 % for intestinal type after 24 months; 30 % and 45 % respectively after 48 months.

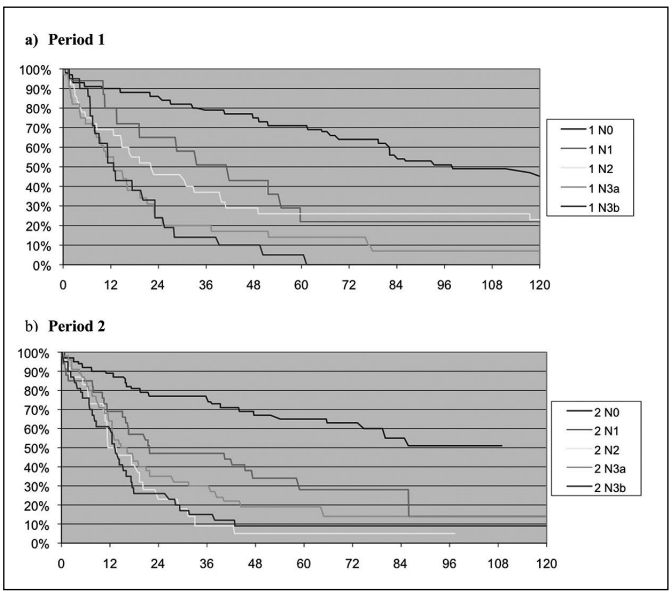

Fig. 2: Overall survival curves for two periods stratified by lymph nodes invasion.

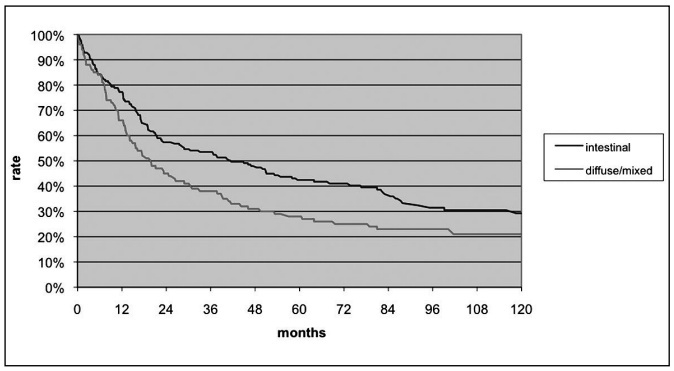

Fig. 3: Overall-survival curves stratified by Lauren histotype.

Discussion and Comments

In this study we retrospectively analysed feasible changes in clinical and histopathological feature, surgical treatment and overall-survival in patients with GC in the last fifteen-years. The most important findings were an increase in lymph node involvement and a decrease in depth of tumor invasion, an higher percentage of whole type and a decrease in palliative surgery. Overall-survival hasn't changed in the last fifteen years.

The main prognostic factor in GC is obviously tumor stage; the recent AJCC classification of the TNM system (7th Edition) modified the definition of pT and pN classification [15]. Prognosis worsens progressively with depth of invasion of gastric wall with a sharp decrease in survival for patients whose tumor perforates the serosa. Lymph nodes involvement is a crucial prognostic factor in GC [16-22]; the number of metastatic lymph node has a deep impact on prognosis such that cut-off values were modified in the new TNM classification [23]. In our paper we demonstrated a decrease in the pT4a – pT4b subgroup and an increase in pT2, pT3 and pN3a – pN3b in period 2; this datum suggests that gastric cancer increased over time lymph node involvement. These results confirm the importance of extent of lymph node dissection in the standard surgical approach of GC; in limited lymphadenectomy (D1 dissection) no information is obtained regarding the extra-perigastric nodes and a complete nodal staging is not possible [19,22,25].

Decrease in pT4a – pT4b was related to an improvement of preoperative work-up.

Temporal trends in the tumor site mainly concerns tumors arising from the gastric body or antrum, while the incidence of tumors of the cardias and upper third of the stomach has been stable or even increasing [5,25-27]. In our analysis there wasn't this change in GC location but there was a significant increase in the rate of whole gastric cancer and of gastric stump in period 2.

The increase of cancer of gastric stump is related to previous sub-total gastrectomy for peptic ulcer when there weren't PPI therapy and anti-H2.

The worldwide declining incidence of GC in mainly due to the decreasing incidence of intestinal tumors, while the incidence of diffuse tumor has been generally stable throughout the world [1-7]; we didn't found any change in trend of Lauren histotype over time. The significant decrease of unclassified type is due to the improvement in histological techniques. The present study has confirmed that Lauren histotype is an important prognostic factor for gastric cancer; overall-survival curves stratified by Lauren histotype showed that survival probability decreased significantly over time in diffuse/mixed type. Overall-survival curves wasn't influenced by histotype in the first ten month after surgery. In this study overall-survival in patients with GC hasn't changed over the last fifteen years. We can analyse that there wasn't an increase in early gastric cancer in period 2; this datum can explain the dismal prognosis of GC in Europe where the average 5-year survival estimate is 25 %. By contrast in Japan 5-years survival is around 66% in patients with primary gastric cancer; the good prognosis achieved in Japan is the result of sustained and remarkable improvements in survival in the last decades due to screening programs for GC.

Conclusion

Overall survival in patients with GC hasn't changed over the last fifteen years. Increase in lymph nodes involvement was found, despite a decrease on depth of tumor invasion. This result and the unchanged rate of overall survival, with an improved quality of limphadenectomy, confirms the worse prognosis of GC related to advanced stage and the need to increase diagnosis of early gastric cancer.

Riassunto

Lo scopo di questo studio è stato analizzare i cambiamenti clinici ed istopatologici del cancro gastrico negli ultimi quindici anni ed analizzare i fattori che influenzano la sopravvivenza globale.

Abbiamo retrospettivamente analizzato i pazienti sottoposti a chirurgia per il cancro gastrico da gennaio 1996 a dicembre 2010. L'analisi si è focalizzata su due periodi: 1996-2003 (periodo 1) e 2004-2010 (periodo 2). Abbiamo riscontrato un incremento dell'età di distribuzione del cancro gastrico nel secondo periodo (p=0.012). Sono emersi lievi ma significativi cambiamenti nello stadio della neoplasia (Sistema di stadiazione TNM - 7 th edizione). Non sono stati rilevati cambiamenti nella sopravvivenza globale negli ultimi quindici anni; mentre è stata riscontrata una prognosi peggiore per il tipo diffuso secondo Lauren. I risultati confermano l'importanza di una linfoadenectomia estesa nel trattamento standard del cancro gastrico. Questo

lavoro conferma la pessima prognosi dei pazienti affetti da cancro gastrico e la necessità di incrementare la diagnosi di questo tumore ad uno stadio precoce.

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