The prognostic role of tumor size in patients with gastric cancer

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AIM: *The identification of prognostic factors in gastric cancer is important for predicting patients' survival and determining therapeutic strategies.*
MATERIALS OF STUDY: *A retrospective analysis ofpatients who underwent surgery for gastric cancer between 1996 and 2010. The appropriate cut-off value of tumor size related to survival was determined using receiver-operating characteristic (ROC) curves and it was 2,5 cm. Patients were divided into three groups: a small size group (SSG, < 2,5 cm), a medium size group (MSG, between 2,5 and 5 cm) and a large size group (LSG, ≥ 5 cm).*
RESULTS: *Depth of invasion and lymph node metastasis resulted significantly related to tumor size ($p < 0.05$). Kaplan-Meier survival curves showed that OS rate was significantly higher in SSG patients. The prognosis of patients with tumor size < 2,5 cm was better than patients with tumors ≥ 2.5 cm in size ($p < 0.01$).*
DISCUSSION: *The tumor size resulted significantly related to OS and it was related to depth of invasion and lymph node metastasis that are themselves prognostic factors. These results confirm and reinforced literature and suggest that at diagnostic pre-operative work-up we can yet define a prognostic value based on tumor size and underline the primary role of complete resection with free surgical margins and D2 lymphadenectomy.*
CONCLUSION: *In patients with gastric cancer tumor size suggests information about the malignancy of the tumor: it is an important predictor of survival and 2,5 cm may be considered as a valid cut-off to define a better or worse prognosis.*

KEY WORDS: Gastric cancer, Prognosis,Survival, Tumor size

Introduction

Despite a decline in incidence and mortality, gastric cancer (GC) remains a neoplasm with a worse prognosis [1]. The identification of prognostic factors in GC is extremely important for predicting patients' survival and determining therapeutic strategies. The end-points usually considered in the evaluation of long-term outcomes of patients with GC are overall survival (OS - deaths from any cause) and cancer-related survival (deaths from GC progression); these factors differ according to several prognostic factors [2]. Usually, prognostic factors can be included in three large categories: 1) tumor-related, 2) patients-related and 3) treatment-related factors [2].
The most important tumor-related prognostic factor is doubtless tumor stage [2-4]: the 7th edition of the TNM stage system modified the definition of pT and pN classifications as well as the stage grouping and introduced new parameter for M stage (peritoneal cytology) [2,5]. In literature many studies indicate that the depth of inva-

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sion (pT) and the presence or absence of lymph node metastasis (pN) are crucial prognostic factors 6-8: prognosis worsens more and more with depth of the invasion of the gastric wall, with a wide decrease in survival for patients whose tumor perforates the serosa [2,5-10]; in patients in which tumor involves adjacent organs the prognosis is poor even after potentially curative surgery (R0 resection in lymph node [2,8,11,12]. Lymph node involvement is the other most important prognostic factor in GC: the number of metastatic nodes has a considerable impact on prognosis such that the cut-off values were changed in the 7th edition of TNM classification [2,3,5,7].

The presence of distant metastases and of tumor cells in the peritoneal washing (pM1 and then Stage IV in the new TNM classification) is also associated with unfavourable outcome in patients with GC [2,5].

The Lauren histotype (intestinal, diffuse or mixed type) seems to be a further useful element in the definition of outcome in GC patients: the diffuse-mixed types have a greater tendency to peritoneal dissemination, particularly when the serosa is involved; whereas the risk of liver metastases is higher in the intestinal type [2,4,10,13].

Tumor size was long disregarded as an independent prognostic factor in GC and, even if its significance is still uncertain in this tumor, its prognostic value is broadly connected to tumor stage: large tumors are frequently histologically poorly differentiated (diffuse/mixed Lauren histotype), have infiltrative growth with penetration of the serosa and have high incidence of recurrence [2,13-15].

Lymphatic and venous invasion in GC have also an important prognostic role [2,16].

Patient-related prognostic factors include age, geographic area and patient's ethnicity [2]. Commonly, advanced age is related to lower OS and cancer-related survival [17,18]; although a lot of Authors reported that younger age (< 45 years) is related to worse prognosis [19].

In literature several studies from the US underline a better outcome in Asian Americans patients with GC than in other ethnicities [20]; Marrelli et al. documented the different prognosis of patients with GC coming from different risk areas of Italy but treated at the same center: they suggested that patients coming from low-risk area of Italy (Southern Italy) show distinct pathological features, more advanced stage and worse prognosis when compared with patients coming from high-risk area (Tuscany) [21].

The most important treated-related prognostic factor is surgical radicality: R0 resection (complete tumor removal without micro or macroscopic residual disease) with D2 lymphadenectomy [22,23]. Perioperative and postoperative combination therapy became the established treatment of GC: a lot of trials from America [24] and from Europe [25] demonstrated 5 years survival advantages in patients receiving chemotherapy before and after surgery [26].

In this paper we focused on the prognostic significance of tumor size, given as the maximum diameter of the tumor that can be easily measured before or during surgery without special tools.

Materials and Methods

This study is a retrospective analysis of 463 patients who underwent surgery for confirmed primary gastric adenocarcinoma between January 1996 and December 2010 at Operative Unit General Surgery and Organ Transplantation, University Hospital of Parma.

The analysis focused on 346 patients that underwent curative surgery: the curative surgery was defined as a complete absence of grossly visible tumor tissue and pathologically negative resection margins performed in M0 patients who underwent lymph node dissection (D1 or D2 lymphadenectomy) according to AJCC/IUCC 7th Edition 2010 TNM stage. In case of adjacent organ invasion of T4b, combined resection was carried out and the resection margin must be negative. Explorative laparotomy and bypass procedures were excluded from this study.

Eligibility criteria included: histologically proven primary adenocarcinoma of the stomach; no history of gastric surgery; absence of non-curative surgical factors such as distant metastasis, peritoneal dissemination, unresectable bulky lymph node metastasis; pathologically negative resection margins (R0 resection); remaining alive in the first 30-days after surgery.

Before surgery all patients underwent upper gastrointestinal endoscopy with biopsy and chest and abdominal computerised tomography scan (CT-scan) with contrast to evaluate the location, diameter and invasion depth of the tumor, as well as the status of lymph node and distant metastasis.

Staging of neoplasms was performed according to American Joint Committee on Cancer (AJCC) / TNM Staging Classification for the Carcinoma of the Stomach (7th Edition, 2010) [3].

Data were retrieved from patients' operative and pathological reports and we created a dedicated retrospective database in which we organized clinical and histopathological features. Data included sex, age (< 70 years or ³ 70), tumor location (upper, middle, lower and whole), Lauren histotype (intestinal or diffuse type)[27], type of surgery (total gastrectomy or gastric resection), combined resection (yes or no), depth of invasion, lymph node status according to 7th American Joint Committee on Cancer – AJCC.

All patients didn't receive neo-adjuvant therapy and adjuvant therapy wasn't considered in this work.

Tumor size was measured opening the stomach along the greater curvature; only when the tumor was located in the greater curvature the specimen was opened along the lesser curvature. The dissected stomach was then fixed on a flat board and the maximum tumor diameter was macroscopically determined with a ruler as accurately as possible.

The appropriate cut-off value of tumor size related to long-term survival was determined using receiver-operating characteristic (ROC) curve and it was 2,5 cm. Based on this result and according to literature [28-30] patients were divided into three groups as follow: a small size group (SSG, tumor size < 2,5 cm), a medium size group (MSG, tumor size between 2,5 and 5 cm) and a large size group (LSG > 5 cm).
Patient follow–up lasted until death or the cut-off date of November 2015. Survival status was collected through the Parma's Register of Tumors and some data were recorded by contacting the patients directly by phone.

Statistical Analysis

The association of clinico-pathological factors was evaluated by c^2 test.
OS was calculated by Kaplan-Meier method and difference between survival curves were examined with log rank test.
A stratified univariate and multivariate analysis of tumor size, stage pT and pN were performed to evaluate the impact of these factors on prognosis.
$P < 0.05$ 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

This study comprised 203 men and 143 women aged from 33 to 92 years; mean age at surgery was 71,6 years (133 patients were < 70 years old and 213 were ³ 70). Of 346 patients, 44 patients had tumors located in the upper third of the stomach, 106 patients had tumors in the middle third, 187 patients had tumors in the lower third and 9 patients had tumors occupied two-thirds or more of the stomach.
Lymph node metastasis were observed in 231 patients; among these patients pN1 was observed in 43 patients, pN2 in 53 patients and pN3 in 135 patients. Total number of lymph nodes dissected was 7761 (mean 20,1 ± 21,1) and the number of positive lymph nodes was 2779 (mean 7,2 ± 9,5).
Partial gastrectomy was performed in 177 patients and subtotal gastrectomy was performed in the other 169 patients. In all patients 15 or more lymph nodes were dissected according to the AJCC/TNM classification and D2 lymphadenectomy was performed in 190 cases.
Combined resection of adjacent organ invasion increased with tumor size: it was performed in 9 cases in SSG, in 19 cases in MSG and in 32 patients with tumor > 5 cm.
According to Lauren classification [27] intestinal histotype tumors were observed in 181 patients, diffuse histotype in 134 and 31 patients, the older cases, were unclassified.

Table I - *Clinical and pathological characteristics of patients divided in three groups according to tumor size. SSG - small size group: tumor size < 2,5 cm; MSG -medium size group: tumor size between 2,5 and 5 cm; LSG - large size group: tumor size ≥ 5 cm.*

	SSG (n)	**MSG** (n)	**LSG** (n)
Sex			
Male	37	68	98
Female	25	50	68
AGE			
Age < 70 years	28	47	58
Age ³ 70 years	34	71	108
Tumor Location			
Upper	6	17	21
Middle	15	30	61
Lower	41	70	76
Whole	0	1	8
Resection Type			
Total gastrectomy	19	51	99
Subtotal gastrectomy	43	67	67
Depth of Invasion			
pT1	36	15	12
pT2	8	19	7
pT3	6	16	25
pT4	12	68	122
Lymph Node Involvement			
pN0	40	38	37
pN1	5	21	17
pN2	7	19	27
pN3	10	40	85

(n): number of patients.

Tumor size ranged from 0,5 cm to 16 cm (Fig. 1). Table I shows clinical and pathological characteristics of patients divided in three groups according to tumor size. There weren't statistically significant differences in tumor location and Lauren histotype in different tumor size subgroups. Sex and age were also not significantly different between three groups analyzed.

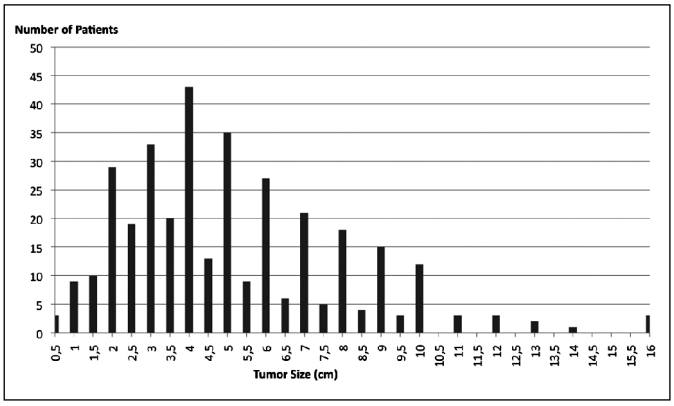

Fig. 1: Patients' distribution according to tumor size.

Total gastrectomy was more frequently carried out in patients with large tumors (SSG: 19 total gastrectomy VS 43 gastric resection; MSG: 51 total gastrectomy VS 67 gastric resection; LSG: 99 total gastrectomy VS 67 gastric resection).
pT and pN resulted significantly related to tumor size ($p < 0.05$). SSG had a larger proportion of pT1 and pN0; conversely MSG and LSG had a larger proportion of pT4 and pN3 (Figs. 2, 3): tumor size resulted an independent prognostic factor for depth of invasion and lymph node status.
The median follow-up period was 50,3 months (1-237 months) (Fig. 4). Shows Kaplan-Meier survival curves of patients divided in three subgroups according to tumor size: OS rate was significantly higher in SSG patients than in MSG and LSG.
The 5-years survival rate was 59% in patients with tumor size < 2,5 cm, 30% in patients with tumor size between 2,5 and 5 cm and 27% in patients with tumor size ³ 5 cm.
These results confirm that tumor size is a strong independent prognostic factor with statistical significance for survival in patients with GC ($p < 0.01$) and particularly 2,5 cm is a valid cut-off for a better or worse prognosis. This cut-off value of 2,5 cm was enhanced by a sensibility of 74,1% and by a specificity of 62%. There wasn't significant difference in survival between MSG and LSG.

Discussion and Comments

Several tumor-related, patient-related and treatment-related prognostic factors were identified for patients with GC. Tumor stage, surgical radicality, tumor location and patient age are the most important conventional prognostic variables. Extended lymphadenectomy and higher number of removed lymph nodes are also related to a better prognosis [2]. The role of other factors is controversial or not generally validated.
According to AJCC/TNM classification the tumor size was included in the classification of disease in lung cancer, breast cancer, thyroid cancer and other cancers [28,29]. However, it was controversial to add tumor size into the GC staging system, even if in recent years a lot of studies underlined tumor size as an indicator influencing prognosis and survival in patients with GC [28-32]. The prognostic role of tumor size in GC has lately received greater attention because it could be determined quite easily in the pre-operative exams or during surgery. There is as yet no consensus standard formula to calculate appropriate cut-off value for gastric tumor size and previous studies classified tumor size on their own standards. In literature, Adachi et al [28] categorized tumor size into three groups (tumors less than 4 cm, tumors

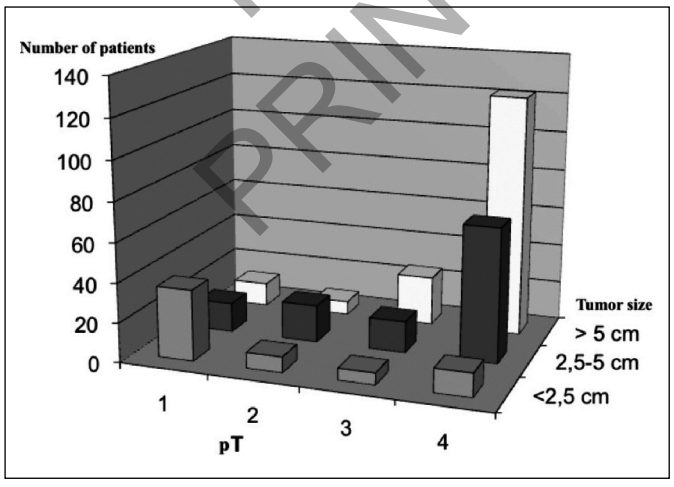

Fig. 2: The correlation between tumor size and depth of wall invasion.

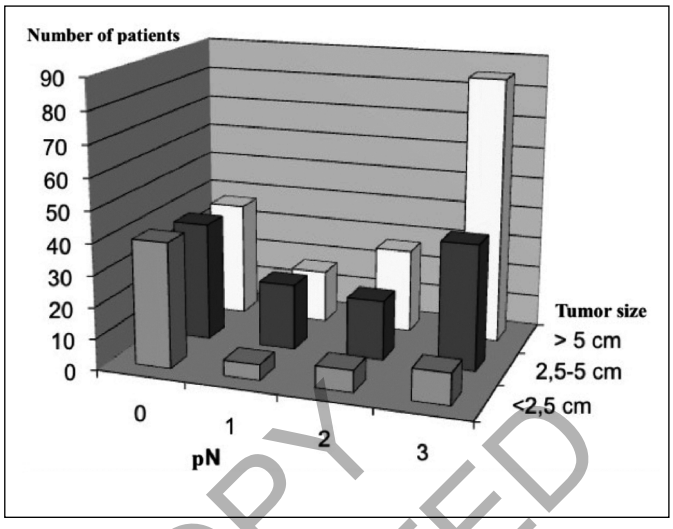

Fig. 3: The correlation between tumor size and presence of lymph node metastasis.

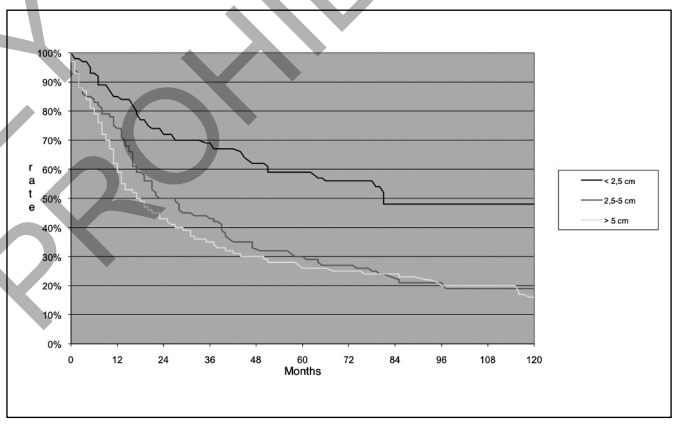

Fig. 4: Kaplan-Meier survival curves of patients divided in three subgroups according to tumor size: OS rate was significantly higher in SSG patients than in MSG and LSG.

between 4 cm to 10 cm and tumors larger than 10 cm) and found that tumor size independently affected the survival of GC patients; however, they didn't provide no data to support the rationale for this grouping. Saito et al [29] divided the maximum diameter by the cut-off of 8 cm and, using the Cox proportional hazard model, pointed out the independent prognostic role of tumor size related to survival. Based on the survival rate, Giuliani et al [33] classified patients into three subgroups: tumors < 26 mm, tumors between 26 and 50 mm and tumors > 50 mm. Wang et al [30] stratified tumor size of GC into four groups (£ 2 cm, £ 3 cm, £ 5 cm and > 5 cm) by using the method of minimizing the estimated average expected distance objective function. Nevertheless, the prognostic role of tumor size in GC should be considered uncertain because some studies found that it was a predictor of survival only in univariate analysis but not in multivariate analysis [33].

In this paper, analysis of ROC curves for tumor size and OS (sensibility=74,1%, specificity=62%) determined that the valid cut-off point is 2,5 cm. ROC analysis is often used in epidemiological and clinical studies to determine a correct cut-off value; however, this issue needs to be further discussed because there is no standard and definitive cut-off of tumor size.

The prognosis of patients with tumor size < 2,5 cm was significantly better than patients with tumors > 2,5 cm in size: tumor size was a strong independent prognostic factor with statistical significance for survival in patients with GC ($p < 0.01$) and particularly 2,5 cm was a valid cut-off for a better or worse prognosis (Fig. 4). According to literature [28-30,33], we also divided patients with tumors > 2.5 in two subgroups (MSG: tumor size between 2,5 and 5 cm; LSG: tumor size ³ 5 cm) but there wasn't significant difference in survival between MSG and LSG.

In our study tumor size was statistically associated with depth of invasion and lymph node metastatic involvement (Figs. 3, 4): compared with SSG, MSG and LSG showed deeper infiltration and were associated with more extensive lymph node metastasis ($p < 0.05$).

We can point put one major consideration about the significance of tumor size.

The tumor size is a strong factor in the evaluation of the prognosis in patients with GC because it was significantly related to OS and because it was related to depth of invasion and lymph node metastasis that are themselves prognostic factors. These results confirm and reinforced literature [28-30,33], suggest that at diagnostic preoperative work-up we may yet define a prognostic value based on tumor size and underline the primary role of complete resection with free surgical margins and D2 lymphadenectomy.

We underline some limitations and drawbacks of this original article. First of all, this study is retrospective and we couldn't consider oncologic therapies: the patients included in this study underwent surgery between 1996 and 2010 and in these years' relevant changes resulted from Intergroup Trials [34] as well as from the Magic Trials [35] in neoadjuvant and adjuvant strategies. We weren't able to include the role of chemotherapeutic treatment in the analysis of OS. We collected the survival status of patients using the Parma's Register of Tumors but we couldn't provide information about the tumor recurrence: this is another limitation of this study. At the end several studies investigated the role of tumor size of GC and some them reported conflicting results.

Multi-centric randomized trials are still needed in the future to better define the correct and standard cut-off value of tumor size, helping to identify the best treatment option and the correct prognosis for patients affected by GC.

Conclusions

According to our analysis tumor size suggests information about the malignancy of the tumor: it is an important predictor of survival in patients with GC and 2,5 cm can be considered as a valid cut-off to define a better or worse prognosis. Tumor size is related to depth of invasion and lymph node metastasis and it should be considered as independent prognostic factor.

Riassunto

L'identificazione di fattori prognostici nei pazienti con cancro gastrico è importante per predire la sopravvivenza e per determinare le successive strategie terapeutiche. Le dimensioni del cancro gastrico sono state a lungo discusse come possibile fattore prognostico indipendente e, anche se il loro ruolo in questa neoplasia non è ancora certo, il loro valore prognostico è risultato essere collegato allo stadio del tumore in molti studi presenti in letteratura. Abbiamo condotto un'analisi retrospettiva su 463 pazienti che sono stati sottoposti a chirurgia per cancro dello stomaco dal 1996 al 2010 presso la Clinica Chirurgica e dei Trapianti d'Organo dell'Azienda Ospedaliero Universitaria di Parma. L'analisi si è poi focalizzata su 346 pazienti che sono stati sottoposti a chirurgia curativa. Abbiamo utilizzato le curva ROC per determinare un appropriato valore cut-off delle dimensioni del cancro gastrico da correlare con la sopravvivenza; questo valore è risultato essere 2,5 cm. I pazienti sono stati quindi suddivisi, anche sulla base della letteratura, in tre gruppi:

a small size group (SSG, dimensioni < 2,5 cm), a medium size group (MSG, dimensioni tra 2,5 e 5 cm) e a large size group (LSG ≥ 5 cm). L'analisi statistica ci ha mostrato correlazione tra le dimensioni del cancro gastrico e l'infiltrazione di parete e la presenza di metastasi linfonodali ($p < 0.05$). Le curve di sopravvivenza sec. Kaplan-Meier hanno dimostrato che la sopravviven-

za è significativamente più alta nei pazienti con cancro gastrico < 2,5 cm. La prognosi dei pazienti con cancro gastrico minore di 2,5 cm è migliore di quella dei pazienti con cancro gastrico superiore a 2,5 cm. Le dimensioni sono un importante fattore prognostico indipendente con significatività statistica sulla sopravvivenza ($p < 0.01$). Questi risultati confermano i dati presenti in letteratura e suggeriscono che già agli esami preoperatori ed in corso di intervento chirurgico possiamo già avere un ulteriore fattore prognostico sulla neoplasia che ci può aiutare anche nella gestione chirurgica della patologia.

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