

Clinicopathological Features and Disease Outcome of Complicated Gastric Cancer with Outlet Obstruction, Perforation or Overt Bleeding. Results of a Retrospective Multicenter Study on Behalf of the Italian Research Group for Gastric Cancer –GIRCG

E. Orsenigo^{1*}, M.C. Salandini¹, L.Graziosi², S. Ministrini³, S. Giacopuzzi⁴, L. Scorsone⁴, S.Sofia⁵, Arianna Coniglio³, R. Reddavid⁵, F. Casella⁶, M. Degiuli⁵, G. De Manzoni⁴, G.A.M. Tiberio³, A. Donini², M. Carlucci¹

¹Department of General and Emergency Surgery, San Raffaele Scientific Institute, Milan, Italy

²Department of General and Emergency surgery, Santa Maria della Misericordia Hospital, Perugia, Italy

³Department of Surgery, Spedali Civili, Brescia, Italy

⁴Department of General and Upper GI Surgery, Ospedale Civile Maggiore, Verona, Italy

⁵Surgical Oncology and Digestive Surgery, San Luigi University Hospital, Orbassano, Turin, Italy

⁶Department of General Surgery, Ospedale M.G. Vannini, Rome, Italy

***Corresponding author:** Elena Orsenigo, Department of General and Emergency Surgery. Chirurgia Generale e d'Urgenza, Via Olgettina, 60; 20132 Milan, Italy. Tel: +39-0226433645; Email: orsenigo.elena@hsr.it

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Abstract

Background: This study aimed to evaluate clinicopathological features, surgical management and disease outcome of gastric cancer with outlet obstruction, perforation or overt bleeding, serious conditions with potentially dangerous effects.

Methods: We retrospectively analyzed data on a consecutive series of 2169 patients submitted to elective and emergency surgery for gastric cancer between 2000 and 2015 in six centers of Italian Research Group for Gastric Cancer (GIRCG).

Results: Out of the 2169 patients, 392 (18%) were complicated gastric (261 were men, 66.6%). The mean age was 71 (SD: 11.3). Gastric cancer with outlet obstruction (GOO) was present in 156 patients (39.8%), perforation in 12 patients (3.1%), and overt bleeding in 224 patients (57%). Comorbidities were present in 74.4% of the patients (n=303). D2 lymphadenectomy was performed in 63.5% cases. The mean number of node retrieved was 30. Node negative patients were 120 (30.6%). Radical surgery (R0) was obtained in 85% of cases (n=334). The overall patient's survival was 80.5%, 45%, 32.5% at 1,3,5 years respectively. Univariate analysis revealed that completeness of tumour removal, type of complicated gastric cancer, type of node dissection, number of node retrieved, nodes involvement, Lauren Classification, and AJCC stage had an effect on survival. At the multivariate analysis, only completeness of tumour removal, type of complicated gastric cancer, type of node dissection, and node metastasis were independent prognostic factors.

Conclusions: The rate of radical resection in complicated gastric cancer was satisfactory with 85% of R0 resections. Completeness of tumour removal, type of complicated gastric cancer, type of node dissection, and nodes involvement were independent prognostic factors for survival.

Keyword: Bleeding; Gastric cancer; Perforation; Stenosis

Introduction

A diagnosis of cancer following a complicated presentation is associated with poorer clinical and patient-reported outcomes. These inferior outcomes include the less-frequent use of treatments with a curative intent, well-established associations between emergency or urgent presentation and inferior survival, and worse quality of life and patient experience than those diagnosed with cancer through other routes [1]. Outlet obstruction, perforation and overt bleeding are ominous complications of gastric cancer. Gastric outlet obstruction was described by Sir, James Walton as “The stomach you can hear, the stomach you can feel and the stomach you can see.” Gastric outlet obstruction implies complete or incomplete obstruction of the distal stomach, pylorus, or proximal duodenum. Once a mechanical obstruction is confirmed, the problem is to differentiate between benign and malignant processes because definitive treatment is based on recognition of the specific underlying cause. The most common cause of gastric outlet obstruction in adults is gastric cancer (63%) and the remaining 37% are due to benign disease [2]. Surgeons should have to take into consideration that repeated vomiting in these patients causes nutritional deficiencies, and occurs with marked dilatation and edematous thickening of the gastric wall. Nutritional deficiency has been regarded as a significant risk factor for postoperative complications in major abdominal surgery [3,4]. Gastric carcinoma with pyloric stenosis, the main source of malignant gastric outlet obstruction, is usually far advanced, and the significance of surgical treatment for such conditions has been given little attention in the literature [5]. Perforated gastric is rare, accounting for 0.3-3% of gastric cancer cases [6]. Only one third of cases of perforated gastric cancer are diagnosed pre-operatively [7,8]. Gastric cancer bleeding accounts for 58% of the bleeding cases resulting from upper gastrointestinal malignancies [9]. The effects of obstruction, perforation, and overt bleeding and the possible simultaneous effects of these conditions on the outcome of gastric carcinoma are difficult to determine because the definitions of these conditions used in previous studies were either imprecise or not stated. Given this lack of clarity about the entities of outlet obstruction, perforation, and overt bleeding in gastric cancer it is not surprising that the impact of these conditions on outcome remains unclear. This multicenter retrospective study evaluated the effect of these conditions on the outcome of gastric carcinoma with clear definitions of outlet obstruction, perforation, and overt bleeding.

Materials and Methods

The cancer registry information and medical charts of all 2169 patients with gastric carcinoma surgically treated with curative intent in six centers of GIRCG (Italian Research Group

of Gastric Cancer) from 2005 to 2015 were reviewed. Out of the 2169 patients, 392 (18%) were complicated gastric cancer patients with GOO, perforation or overt bleeding. GOO was defined as history of vomiting and diet difficulties or foul filled, distended stomach in abdominal radiographs or stasis of food in the stomach or obstruction of the passage of endoscope or absence of passage of contrast medium in the duodenum. Perforation at the site of the cancer was defined as a perforation in the immediate location of the primary tumor. Overt bleeding was defined as hematemesis, melena, haematochezia or gastric cancer confirmed as a source of bleeding by endoscopy. Patients were divided into 3 groups: Group 1, GOO; Group 2, perforation at the site of the cancer; Group 3, overt bleeding. R0 resection indicates a microscopically margin-negative resection, in which no gross or microscopic tumour remains in the primary tumour bed. R1 resection indicates the removal of all macroscopic disease, but microscopic margins are positive for tumour. R2 indicates gross residual disease with gross residual tumour that was not resected (primary tumour, regional nodes, and macroscopic margin involvement) [10]. Complications were highlighted with the Clavien-Dindo classification [11]. Operative mortality was defined as death that occurred within 1 month or operation-related death during hospitalization. Demographic and clinical data on sex, age, histologic type, tumor stage, and long-term follow-up time of more than 5 years were analyzed. The statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 17.0 for Windows (SPSS, Chicago IL, U.S.A). The mean and median rates and ranges were calculated for continuous variables whereas proportions and frequency tables were used to summarize categorical variables. Chi-square (χ^2) test were used to test for the significance of association between the independent (predictor) and dependent (outcome) variables in the categorical variables. The level of significance was considered as $P < 0.05$. Five-year survival probability was calculated with the Kaplan-Meier method and compared by using the log-rank test followed by the multiple comparisons test. Cox regression analysis was used to identify factors associated with survival.

Results

Among the 2169 surgically treated gastric cancer patients in the analysis, 392 were complicated gastric cancers (group 1: 156; group 2: 12; group 3: 224). GOO (Group 1) was present in 156 patients (39.8%) with a mean age of 70.4 years. Perforation (Group 2) was present in 12 patients (3.1%) with a mean age of 69 years. Overt bleeding (Group 3) was present in 224 patients (57%) with a mean age of 72.8 years. Out of the 392 patients with complicated gastric cancer 261 were men (66.6%). The mean and median age was 71.8 and 73.5 years, respectively (min 36, max 94 years) (SD: 11.3). The rate of young patients (<45 years) was 1.8% (n=7). The remaining clinicopathological factors of the patients are shown in (Table 1).

| | | Group 1 (n=156) | Group 2 (n=12) | Group 3 (n=224) | Total 392 | P value |
|------------------------|-----------------------------|-----------------|----------------|-----------------|------------|---------|
| Age, n (%) | <45 | 5 (3.2) | 0 (0) | 2 (0.9) | 7 (1.8) | NS |
| | >45 | 151(96.8) | 12 (100) | 222 (99.1) | 385 (98.2) | |
| | Mean (SD) | 70.74 (11.7) | 69 (13.6) | 72.8 (10.8) | 71.8 | |
| Sex, n (%) | Female | 53 (34) | 9 (75) | 75 (33.5) | 131 (33.4) | NS |
| | Male | 103(66) | 3 (25) | 149 (66.5) | 261 (66.6) | |
| | Comorbidities, n (%) | 115 (73.7) | 7 (58.3) | 181 (80.8) | | |
| Type of surgery | LPS | 18 (11.5) | 0 (0) | 21 (9.4) | | NS |
| | LPT | 138 (88.5) | 12 (100) | 203 (90.6) | | |
| | Pathology* | | | | | |
| Intestinal | | 85 (54.5) | 5(41.7) | 133 (59.4) | 223 (56.9) | 0.05 |
| | Diffuse | 68 (43.6) | 5(41.7) | 81(36.2) | 154 (39.3) | |
| | Mixed | 3 (1.9) | 2 (16.7) | 10 (4.5) | 15 (3.8) | |

*Lauren Classification

Table 1: Clinicopathological data in 392 surgically treated complicated gastric cancer.

Comorbidities were present in 74.4% of the patients (n=303). Neoadjuvant chemotherapy was performed in 58 patients (14.8%). Minimally invasive approach was performed in 39 patients (9.9%). Type of operations were: partial proximal gastrectomy (n=10, 2.6%), Roux-en-Y distal sub-total gastrectomy (n=201; 51.2%), Billroth II distal sub-total gastrectomy (n=23; 5.8%), total gastrectomy (n=132; 33.7%); wedge resection (n=2; 0.5%), esophagogastrectomy (n=9; 2.29%), total gastrectomy after previous surgery for benign disease (n=13; 3.3%), gastroenteroanastomosis (n=2; 0.5%). D1, D1 plus, D2, D3 lymphadenectomy was performed in 24.5%, 4.3%, 63.5% and 7.7% of patients, respectively. The mean number of node retrieved was 30 (SD 18) (min 1, max 124). Node negative patients were 120 (30.6%). In 65 cases a multivisceral resection was performed (16.6%). The overall rate of morbidity was 45.2%. Complications were highlighted with the Clavien-Dindo classification (Table 2).

| Clavien-Dindo | n | % |
|------------------|-----|------|
| Grade 0 | 215 | 54.8 |
| Grade I | 29 | 7.4 |
| Grade II | 103 | 26.3 |
| Grade III | 20 | 5.1 |
| Grade IV | 8 | 2 |
| Grade V | 17 | 4.3 |

Table 2: Clavien-Dindo classification of postoperative complications in 392 surgically treated gastric cancer.

Out of these 392 patients, the overall operative mortality rate was 4.3% (n=17 patients). [Ten out of 156 patients (7.05%) in Group 1, 0 patients out of 12 in Group 2 (0%), and 7 out 226 patients in Group 3 (5.5%)]. Group 1 had a higher operative mortality than Groups 2 and 3 (P=0.032). %). Mean hospital stay was 14.8 days (min 5 days, max 99). The AJCC cancer stages are

depicted in (Table 3). Radical surgery (R0) was obtained in 85% of cases (n=334). The follow-up ranged from 1 to 156 months (mean: 26 months). The overall patient's survival was 80.5%, 45%, 32.5% at 1,3,5 years respectively. The patient 5-year survival was 19%, 33%, and 43% in Group 1, Group 2, and Group 3, respectively; (log rank<0.0001). Univariate analysis revealed that completeness of tumour removal, type of complicated gastric cancer, type of node dissection, and number of node retrieved, node involvement (N+), Lauren Classification, and AJCC stage had an effect on survival (Table 4). An AJCC stage \geq III was present in 70.7%, 33%, and 52% of cases in group 1, 2 and 3, respectively. Factors influence survival at the univariate analysis were entered in a Cox regression model. Based on multivariate analysis completeness of tumour removal, type of complicated gastric cancer, type of node dissection, node involvement was determined to be independent prognostic factors (Table 5).

| AJCC stage | n (%) |
|-------------|-----------|
| 0 | 5 (1.3) |
| IA | 19 (4.8) |
| IB | 30 (7.7) |
| IIA | 51 (13) |
| IIB | 35 (8.9) |
| IIIA | 64 (16.3) |
| IIIB | 76 (19.3) |
| IIIC | 49 (12.5) |
| IV | 63 (16.2) |

Table 3: AJCC cancer stage (n=392 complicated gastric cancer with outlet obstruction, perforation and overt bleeding).

| | P value |
|---|---------|
| Age | NS |
| Sex | NS |
| Completeness of tumor removal (R0 vs R1 vs R2) | 0.013 |
| Type of complicated gastric cancer[°] | 0.0001 |
| Type of surgery (LPS vs LPT) | 0.566 |
| Type of node dissection (D1vs D1 plus vs D2 vs D3) | 0.005 |
| Number of node retrieved | 0.035 |
| N0 vs N+ | 0.0001 |
| Pathology[*] | 0.01 |
| AJCC stage | 0.001 |

[°]outlet obstruction vs perforation vs overt bleeding; ^{*}Lauren Classification.

Table 4: Univariate analysis of different parameters for survival in 392 surgically treated complicated gastric cancer.

| | P value |
|--|---------|
| Completeness of tumor removal (R0 vs R1 vs R2) | 0.0001 |
| Type of complicated gastric cancer[°] | 0.0001 |
| Type of node dissection (D1 vs D1 plus vs D2 vs D3) | 0.033 |
| Number of node retrieved | NS |
| N0 vs N+ | 0.0001 |
| Pathology[*] | NS |
| AJCC stage | NS |

[°]outlet obstruction vs perforation vs overt bleeding; ^{*}Lauren Classification

Table 5: Multivariate analysis of different parameters for survival in surgically treated complicated gastric cancer.

Discussion

The majority of the patients present with non-acute symptoms but gastric cancer can also manifest as an emergency or urgent presentation with overt bleeding, visceral perforation, or gastric outlet obstruction. Complicated presentation of gastric cancer has been shown to have an influence on overall survival, which is independent to any other factors. Blackshaw, et al. [12] showed that patients presenting as an emergency had a median survival of 6 months, compared to 12 months for patients referred as an outpatient. Therefore, although emergency or urgent presentation is relatively rare, it may significantly affect prognosis and continues to be associated with higher stage of disease at presentation and lower rates of operability. Emergency or urgent operative intervention in gastric cancer is usually required in patients with GOO, perforation or over bleeding. Cancer arising in the distal third where the luminal diameter of the stomach progressively narrows may cause gastric outlet obstruction. The majority of studies on this subject have focused on the value of palliative gastrectomy [13,14], or have compared the merits of bypass surgery versus endoscopic stents in terms of relieving GOO in the setting of metastatic diseases [15,16]. However, outcomes of radical surgery for gastric carcinoma with GOO have not been well established. Preoperative GOO due to advanced lesion involving prepyloric region may increase the incidence of duodenal stump leakage [17,18]. Perforation of gastric cancer results in an acute abdominal syndrome due to leakage of gastric contents and the consequent peritonitis. It is often difficult to recognize the type of lesion that caused gastric perforation at the time of emergency surgery, particularly when pathological evaluation of frozen sections cannot be performed. Under such conditions, the surgeon should diagnose the cause of perforation on the basis of rigidity

of the gastric wall and lymph nodes, size of ulceration and the presence of metastasis in the liver and peritoneum [19]. Treatment decisions for the surgeon confronted with a gastric perforation revolve around the management of life threatening sepsis and the extent of intervention. Surgical management requires consideration of patient factors, such as hemodynamic stability and pre-existing co-morbidities, as well as the extent of disease and contamination. The surgeon must choose between non-oncologic procedures, such as simple closure and emergent simple resection, and more extensive oncologic resections that may not be well tolerated in the setting of perforation. Simple closure of the perforation has historically been associated with poor results [20]. A two- stage surgical approach for perforation in the setting of gastric cancer was identified in the literature, which includes simple closure or gastrectomy as the first stage, followed by definitive gastric cancer resection in an elective setting [21,22]. Nevertheless, curative

gastrectomy is undoubtedly the preferred treatment for perforated gastric cancer. Minor bleeding is a well-known characteristic of gastric cancer, often causing chronic microcytic hypochromic anemia, prompting gastroscopy. However, gastric cancer can also present with major bleeding in up to 5% of patients. These patients may require blood transfusion to prevent hemodynamic compromise. Endoscopic therapy can be used to control bleeding with the use of injection of adrenaline to the tumor base, argon plasma coagulation or with application of endo-clips [23]. However, patients may require surgery for bleeding control if endoscopic measures for hemostasis fail. The aim of our study was mainly the analysis of clinicopathological features, treatment and oncological outcome in 392 cases of complicated gastric cancer surgically treated with curative intent during January 2000 and December 2015 in six centers of GIRCG (Italian Research Group for Gastric Cancer) (Figure 1).

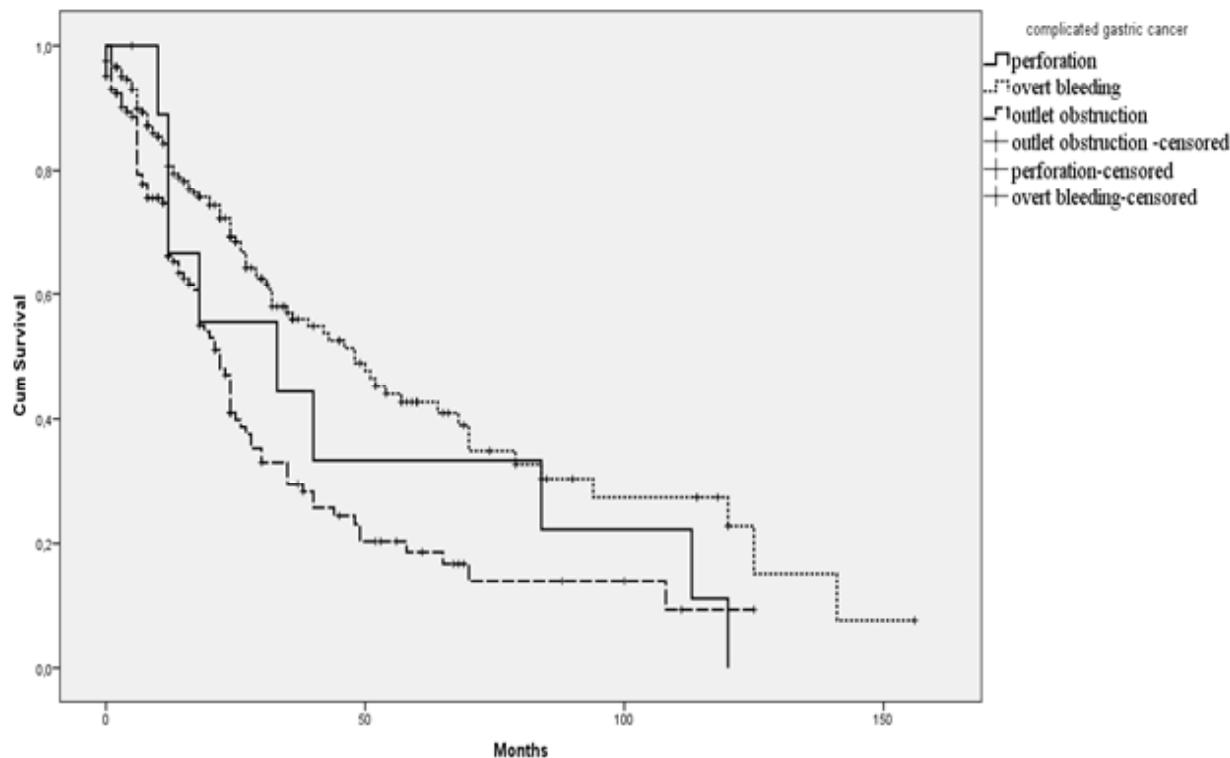


Figure 1: Survival in 392 surgically treated complicated gastric cancer (log rank<0.0001).

Out of 392 cases

Gastric carcinoma with outlet obstruction: 156 cases (Group 1)

Gastric carcinoma with perforation: 12 cases (Group 2)

Gastric carcinoma with overt bleeding: 224 cases (Group 3)

Regarding patient demographic data of our series we have to underline that complicated gastric cancer is more frequent in men (66.6%) and in elderly patients (mean age: 71.8) and very rare in young patient (1.8% cases <45 years). Due to this distribution in elderly patients, the rate of comorbidities was incredibly high (74.4% of the patients), without differences among the three groups. Comorbidity has been reported to be a predictor of post-operative complications in patients who receive gastrectomy for gastric cancer [24-27]. This finding and the influence of complicated gastric cancer could explain the high morbidity rate (45.2%) in our study. Nevertheless, 33.7% were postoperative complications Clavien-Dindo Grade I-II and 2% Grade IV. Out of these 392 patients, the overall operative mortality rate was 4.3% (n=17 patients) and Group 1 had a higher operative mortality than Groups 2 and 3 ($P=0.032$). Neoadjuvant chemotherapy was performed in only 14.8% of the patients (n=58). There are numerous purported, and some proven, advantages of a neoadjuvant approach-particularly chemotherapy-in the treatment of advanced gastric cancer. Early treatment of distant microscopic disease, the ability to gauge *in vivo* response to therapy, and the potential for tumour downstaging to enhance resectability are frequently involved and may translate to better outcomes. A neoadjuvant strategy may increase the likelihood of completing multimodality therapy of gastric cancer, particularly when surgical management is associated with significant morbidity and complications may preclude timely adjuvant therapy. Unfortunately, in our series, despite the high rate of node involvement (69.4%) and AJCC stage \geq IIA in 86.2% of the cases, neoadjuvant chemotherapy was rarely employed. Reasons for that was the frequent contraindication to this approach in presence of complicated gastric cancer as defined in our study. The mean length of hospital stay was 14.8 days. The average length of stay in hospitals is often used as an indicator of efficiency. A shorter stay may reduce the cost per discharge and shift care from inpatient to less expensive post-acute settings, but we have to take into the account that more of our patients were elderly and suffered from complicated gastric cancer. Out of 392 patients with complicated gastric cancer submitted to surgery with curative intent non resectable cancer was found in only 2 cases (0.5%) and radical resection (R0) was obtained in 85% of cases. Minimally invasive gastric surgery was performed in only 39 patients (9.9%) because complicated gastric cancer frequently not allows this approach. Moreover, the rate of node negative Early Gastric Cancer (EGC) in this study population was very low and according to GIRCG (Italian Research Group for Gastric Cancer)

guidelines for gastric cancer staging and treatment [28] we have reserved laparoscopic gastric resection as an option to consider in patients with EGC. D2 lymphadenectomy was performed in 63.5% of the cases. The mean number of node retrieved was 30, confirming that curative resection was the aim of the surgical approach. The follow-up ranged from 1 to 156 months (mean: 26 months). The overall patient's survival was 80.5%, 45%, 32, 5% at 1, 3, 5 years respectively. The patient 5-year survival was 19%, 33%, and 43% in Group 1, Group 2, and Group 3, respectively; ($\log \text{rank} < 0.0001$). The long-term survival of patients with outlet obstruction was particularly low due to the fact that GOO is usually diagnosed at an advanced stage with aggressive pathological features [29]. In our series an AJCC stage \geq III was present in 70.7%, 33%, and 52% of cases in group 1, 2, and 3, respectively. Univariate analysis revealed that completeness of tumour removal, type of complicated gastric cancer, type of node dissection, number of node retrieved, node involvement (N+), Lauren Classification, and AJCC stage had an effect on survival. Factors influence survival at the univariate analysis were entered in a Cox regression model. Based on multivariate analysis completeness of tumour removal, type of complicated gastric cancer, type of node dissection, node involvement was determined to be independent prognostic factors.

Conclusions

Gastric cancer presenting with complications such as outlet obstruction, perforation and overt bleeding is present in 18% surgically treated with curative intent gastric cancer patients. Carefully selected patients may benefit from an aggressive surgical intervention that addresses both the complication and the malignancy. Radical surgery can be performed in these patients with acceptable mortality. Independent prognostic factors are: completeness of tumour removal, type of complicated gastric cancer, type of node dissection, and node involvement.

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