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EPIDEMIOLOGICAL PROFILE OF SURGICAL PATIENTS WITH GASTRIC CANCER

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Abstract: Gastric cancer worldwide is the fifth most common cancer and has the third highest cancer related mortality. Approximately 8% of total cases and 10% of annual cancer deaths worldwide are attributed to gastric cancer. The symptoms of GC are not pathognomonic and can include loss of appetite and weight, anemia, abdominal pain, early satiety, gastrointestinal bleedings, constipation, diarrhea, indigestion, vomiting, pyrosis, dysphagia, swelling of supraclavicular lymph nodes, and nodules in epigastric and umbilical regions. The diagnosis of GC is carried out through clinical evaluation followed by upper gastrointestinal endoscopy and biopsy. Curative treatment includes surgical resection but comes with risk of complications and the optimal surgery including extent of lymphadenectomy has evolved over time. Surgical resection combined with D2 lymphadenectomy has become the standard treatment for curable gastric cancer; however, it brings a simultaneous increase in surgical complication. The presence or absence of complications was found to be an important factor that can influence the prognosis of patients following curative gastrectomy. Precise grading of complications is essential for analysis of surgical outcomes.

Keywords: Gastrectomy, surgical complications, gastric cancer, risk factors.

Introduction

Gastric cancer (GC) is a globally relevant disease. It is the fifth most common neoplasm and the third most lethal in the world, being associated with more than 780,000 deaths in 2018. Developed countries tend to have a higher GC incidence, especially those located in Asia. GC development is associated with modifiable and non-modifiable risk factors, including Helicobacter pylori infection, unhealthy eating and lifestyle habits, advanced age, male gender, and low socioeconomic status [1]. GC prevention involves H. pylori eradication, elimination of bad habits, and the use of screening methods. The classification systems for GC developed by the World Health Organization, Lauren, and Ming are the most used for GC staging and take into consideration the anatomical and histological characteristics. Furthermore, the recent characterization of the GC molecular profile has led to the proposal of new classification subgroups. The symptoms of GC are not pathognomonic and can include loss of appetite and weight, anemia, abdominal pain, early satiety, gastrointestinal bleedings, constipation, diarrhea, indigestion, vomiting, pyrosis, dysphagia, swelling of

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supraclavicular lymph nodes, and nodules in epigastric and umbilical regions. The diagnosis of GC is carried out through clinical evaluation followed by upper gastrointestinal endoscopy and biopsy. Computed tomography and endoscopic ultrasound are important diagnostic methods for the assessment of the disease. Moreover, the use of tumor markers as a diagnostic technique might be a possibility; however, more studies are needed to evaluate its accuracy. There is no universally recommended standard for the treatment of GC. Surgery is considered a potentially curative method. However, the association with a multimodal approach, such as chemotherapy and chemoradiotherapy, is strategic for improving survival.

Anatomopathological Classifications

The main GC classification systems are those proposed by the World Health Organization (WHO), Lauren, and Ming [2].

According to the WHO, gastric adenocarcinoma is separated into subgroups that include papillary, tubular, mucinous, and mixed carcinoma. The poorly cohesive carcinoma type includes the signet ring cell carcinoma [3].

Lauren's classification is the most useful and widely applied in GC [4]. According to this system, most gastric cancers are adenocarcinomas and present two main histological types: intestinal and diffuse; besides the indeterminate type [5]. The intestinal type is originated from chronic inflammation and progresses via a chronic gastritis-atrophy/metaplasia-dysplasia-carcinoma sequence [6], whereas the diffuse type is composed by separated single cells or small clusters of cells which diffusely infiltrate the layers of the gastric wall [7].

The Ming's classification separates GC into expansive and infiltrative types. The first grows in mass and by expansion, resulting in the tumor nodules, whereas, in infiltrative carcinoma, tumor cells invade the gastric wall individually [8].

Furthermore, based on the recent characterization of the GC molecular profile, four new subgroups have been proposed for the diagnosis and classification of the disease [9]. The Epstein-Barr virus-associated GC (EBVaGC) is one of those subgroups and results from the neoplastic infection caused by EBV that leads to clonal growth of infected epithelial cells as well as to atrophic gastritis [10]. Global hypermethylation of CpG island in EBVaGC induces epigenetic silencing of tumor suppressor genes and seems to be crucial for carcinogenesis [11]. Thus, considering that EBV infection is associated with about 10% of GC cases, serological screening for EBV-specific immunoglobulins was supposed to be useful in the identification of groups with a high GC risk. However, increased prevalence of EBV previous exposure and lack of more accurate markers are still a challenge for achieving that purpose

[12]. The chromosomally unstable carcinomas represent another GC subgroup, and certain copy-number alterations are associated with specific histological types. While copynumber gains at 8q, 17q, and 20q are usually associated with the intestinal type, gains at 12q and 13q are commonly related to the diffuse type [13]. Microsatellite unstable tumors compose another subgroup characterized by elevated mutation rates, including mutations of genes encoding targetable oncogenic signaling proteins. Finally, the genomically stable tumors are associated with the diffuse histological variant and occasional mutations [14].

Material and methods

This is a retrospective study that includes 140 patients operated during a period of time January 2016 - December 2018 in the third clinic of the surgical service of the University Hospital Center "Mother Teresa". Sociodemographic and clinical data were collected for each patient.

Data collection was based on a form where the main variables were used:

- Age
- Date of intervention/Date of admission/Date of discharge
- Gender
- Admission diagnosis/Interventional diagnosis
- The intervention carried out
- Reconstructive method
- TNM staging
- Description of definitive biopsy

Statistical analysis

The statistical program STATA 13.0 was used for data analysis

Categorical variables were presented according to their absolute and relative frequency expressed as a percentage, and the Chi-square ($\chi 2$) statistical test and Fisher's exact test were used for their comparison.

Continuous data are presented with mean (M) and standard deviation (SD).

Student's t-test and ANOVA were used to compare the means of continuous variables.

Statistical significance is defined for $p \leq 0.05$.

Statistical tests are two-sided.

Results

140 patients with a mean age of 66.1 (±11.9) years, ranging from 29 to 97 years, participated in the study. Male patients predominate with 101 cases or 72.1% of the total compared to 39 females or 27.9% of the total. The male / female ratio is 2.6:1.

The age group of 61-70 years dominates with 32.1% of the total, followed by the age group of 71-80 years, 29.3%, with a significant difference with the other age groups, ($p<0.01$). Table 1. shows the sociodemographic characteristics of patients.

Table 1. Sociodemographic characteristics of patients

Variables	N	%	P
Gender			
Female	39	27.9	<0.01
Male	101	72.1	
Age, M (SD)	66.1 (±11.9)	29-97	
Agegroup, yrs			<0.01
≤30	1	0.7	
31-40	3	2.1	
41-50	10	7.1	
51-60	28	20.0	
61-70	45	32.1	
71-80	41	29.3	
>80	12	8.6	
Year			0.5
2016	50	35.7	
2017	41	29.3	
2018	49	35.0	

No significant difference was found in the distribution according to gender and age group ($p=0.3$).

The average age of women is 63.8 (±13.2) years, while that of men is 67.0 (±11.4) years, with no significant difference between them ($p=0.4$).

In 2016, there were 50 cases or 35.7% of the total, followed by 41 (29.3%) cases in 2017 and 49 (35%) cases in 2018, with no significant difference between them ($p=0.5$).

In this study, we presented the anatomical localization according to 4 regions of the stomach: Antral, corpus ventriculi, cardias and gastric stump. It is noted that the most frequent localization is Antrum 52 patients or 37.1% of cases, followed by cardia with 46 (32.8%) cases, corpus with 39 (27.8%) cases and Cungu with 3 (2.1%) cases. Table 2 shows the localization of neoplasia according to anatomical regions of the stomach.

Table 2. Localization of neoplasia according to anatomical regions of the stomach

Localization	**N**	**%**
Cardias	46	32.8
Corpus	39	27.8
Antrum	52	37.1
Gastric stub	3	2.1
Total	140	100.0

The histology of the gastric tumor has an important role in determining the type of intervention but also in the prognosis of the disease. The determination of the histology of gastric tumors was carried out by evaluating the postoperative biopsies of the gastric mass in cases with curative resections. Whereas in inoperable cases and palliative interventions, formations from the mass or lymph nodes or infiltrated organs around were taken for biopsy. From these data, it can be seen that the dominant histological form is adenocarcinoma with 132 cases or 94.3% of patients, followed by Carcinoma with cells like a stone ring or 'signet ring' with 10 cases or 3.6% of patients and GIST with 3 cases, i.e. 2.1 % of patients. So as can be seen we have a predominance of the histological form of adenocarcinoma ($p<0.01$). Table 3 shows the histopathology of gastric tumors.

Table 3. Histopathology of gastric tumors

Histological form	N	%
Adenocarcinoma	132	94.3
Carcinoma’signet ring’	5	3.6
GIST	3	2.1
Total	140	100.0

The average stay of patients is 11.5 (±6.9) days. The days of hospital stay of patients vary from 2-4 days for patients with exploratory laparotomy, 5-7 days for palliative interventions

to 21-25 days for patients with complications. The average length of stay for patients who have undergone gastric resection and curative reconstructive procedures is 11-13 days.

Discussion

The only curative treatment for GC is surgical excision of tumorous mass [53, 54]. Usually abdominal exploration is considered with the curative intent unless there is doubt regarding dissemination, vascular invasion, patient has a medical contraindication for surgery, or a neoadjuvant therapy is considered.

Linitis plastica: In ~5 percent of GC, most of the stomach wall or sometimes the entire stomach wall is infiltrated by malignancy resulting in a rigid thickened wall called linitis plastica. It is more prevalent in younger population [15]. Sometimes this form of cancer represents spread from lobular breast cancer, and is associated with poor prognosis [16]. As there will be nodal involvement frequently, complete excision is the goal even though surgeons consider it to be a contraindication to curative resection.

Total versus subtotal gastrectomy: Total gastrectomy is in vogue for the treatment of invasive GC, even though endoscopic resection is performed for superficial cancers. To note, total gastrectomy is indicated for lesions in the proximal (i.e. upper third) of the stomach, and distal lesions (lower two-thirds) require subtotal gastrectomy with resection of adjacent lymph nodes. Importantly, the patients presenting with large mid gastric or infiltrative lesions like linitis plastica require total gastrectomy.

Proximal and esophagogastric junction tumors: The precise guidelines for surgical excision of proximal tumors are complex. Those tumors that do not invade the esophagogastric junction (EGJ) are managed by either a total or a proximal subtotal gastrectomy. Most surgeons prefer total gastrectomy for the following reasons: 1. The incidence of reflux esophagitis is extremely low following Roux-en-Y reconstruction performed during total gastrectomy compared to those who have undergone proximal subtotal gastrectomy in whom roughly one third patients had reflux esophagitis. 2. It is highly unlikely to remove the lymph nodes along the lesser curvature following proximal subtotal gastrectomy. This may make the metastases escape from surgery.

Degree of lymph node dissection: Again this is the controversial area in the surgical management of GC. Japanese surgeons routinely perform extended lymphadenectomy, which may partially account for the better survival rates among Asian series as compared to Western series [17]. 'Extended lymphadenectomy' refers to either a D2 or D3 nodal dissection.

D1, D2, and D3 terminologies: Japanese surgeons have divided the draining lymph nodes of stomach into 16 stations: stations 1-6 are perigastric, remaining 10 are located side by the major vessels, posterior to pancreas and along the aorta. D1 lymphadenectomy involves limited dissection of only the perigastric lymph nodes. D2 lymphadenectomy involves extended lymph node dissection encompassing removal of nodes along the hepatic, left gastric, celiac and splenic arteries and splenic hilum (stations 1 to 11). D3 lymphadenectomy involves super extended lymph node dissection. In short it is the D2 lymphadenectomy along with resection of nodes within portahepatis and periaortic regions (referred to as stations 1 to 16). Others use the term to denote a D2 dissection plus periaortic nodal dissection (PAND) [18].

Factors in favor of extended lymphadenectomy are, removing more number of nodes accurately stages the disease extent and failure to remove these nodes leaves behind the disease in nearly one third of patients [60]. This would explain the better stage specific survival rates in Asian patients.

Factors against the extended lymphadenectomy are, higher incidence of associated morbidity and mortality especially if splenectomy if done so as to achieve extended lymphadenectomy. Also, most of the randomized trials have shown low survival benefits which discourage surgeons to go for extended lymphadenectomy.

Conclusion

In summary, considering the impact of D2 lymphadenectomy on disease specific survival, most of the cancer hospitals perform D2 as compared to D1 dissection. National Comprehensive Cancer Network has published its treatment guidelines, according to which D2 node dissection is better than D1 dissection. Considering the higher rates of operative mortality in randomized trials, the choice of surgery is at the discretion of the surgeon. D2 lymphadenectomy that preserves pancreas and spleen provides superior staging benefit at the same time avoiding excess morbidity. If splenectomy performed during resection of gastric tumors not adjacent to or invading the spleen or the pancreatic tail will increase the morbidity and mortality without improving the surviva. Hence splenectomy is not recommendable unless the tumor has extended directly.

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