ORIGINAL ARTICLE
doi: 10.35366/111508

Cirujano General
April-June 2023
Vol. 45, no. 2 / p. 76-81

Gastrointestinal stromal tumors: experience in an oncology unit

Tumores del estroma gastrointestinal: experiencia en una Unidad de Oncología

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Keywords: gastrointestinal stromal tumor, stromal tumor, KIT protein, gastrointestinal tract, treatment.

Palabras clave: *tumor del estroma gastrointestinal, tumor estromal, proteína KIT, tubo digestivo, tratamiento.*

ABSTRACT

Introduction: gastrointestinal stromal tumors are the most common mesenchymal tumors and can occur in any part of the digestive tract. **Objective:** to present the 10-year experience in the Oncology Unit of the General Hospital of Puebla "Dr. Eduardo Vázquez Navarro" in managing patients diagnosed with gastrointestinal stromal tumors. **Material and methods:** a longitudinal, retrospective, observational, and clinical study carried out in patients with histopathological diagnosis of gastrointestinal stromal tumors between January 2012 and December 2022 in the Oncology Unit of the General Hospital of Puebla es presented. **Discussion:** 24 files of patients with a diagnosis of gastrointestinal stromal tumor were reviewed. An institutional incidence of 2% was observed. The average age at diagnosis was 53 years, with a male predominance. Surgical treatment was performed in 96% of the cases. A five-year survival of 16% was found, and recurrence was present in 16% of the liver and lungs. **Conclusions:** gastrointestinal stromal tumors have unpredictable behavior. Surgery in the early stages is the curative treatment. Their indolent presentation makes their diagnosis difficult until the advanced stages of the disease. Tyrosine kinase inhibitors have improved survival and are a therapeutic option in cases where surgery is impossible.

RESUMEN

Introducción: *los tumores del estroma gastrointestinal son los tumores mesenquimales más comunes y pueden presentarse en cualquier parte del tracto digestivo.* ***Objetivo:*** *exponer la experiencia de 10 años en la Unidad de Oncología del Hospital General de Puebla "Dr. Eduardo Vázquez Navarro" en el manejo de pacientes con diagnóstico de tumores del estroma gastrointestinal.* ***Material y métodos:*** *estudio longitudinal, retrospectivo, observacional y clínico efectuado en pacientes con diagnóstico histopatológico de tumores del estroma gastrointestinal entre los meses de enero 2012 y diciembre 2022 en la Unidad de Oncología del Hospital General de Puebla.* ***Discusión:*** *se revisaron 24 expedientes de pacientes con diagnóstico de tumor del estroma gastrointestinal. Se observó una incidencia institucional de 2%. El promedio de edad al momento del diagnóstico fue de 53 años, con predominio masculino. Se realizó tratamiento quirúrgico en 96% de los casos. Se encontró una supervivencia a cinco años de 16% y se presentó recurrencia de 16% en hígado y pulmón.* ***Conclusiones:*** *los tumores del estroma gastrointestinal tienen un comportamiento impredecible. La cirugía en etapas tempranas es el tratamiento curativo. Su presentación indolente dificulta su diagnóstico hasta etapas avanzadas de la enfermedad. Los inhibidores de tirosina cinasa han mejorado la supervivencia y son una opción terapéutica en casos en los que no es posible realizar la cirugía.*

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Received: 03/08/2023
Accepted: 05/02/2023

INTRODUCTION

Gastrointestinal stromal tumors were described under this term starting in 1983 and recognized as a heterogeneous gastrointestinal tumor entity; this term was used to refer to this group of neoplasms of mesenchymal origin.[1] This type of tumor represents 1% of the neoplasms of the gastrointestinal tract, with an approximate

How to cite: Pinedo-Vega ÁD, Orea-Estudillo D, Alquicira-Alcántara E, Pérez-Soriano A, Flores-Huerta FF, González-Xicoténcatl J, et al. Gastrointestinal stromal tumors: experience in an oncology unit. Cir Gen. 2023; 45 (2): 76-81. https://dx.doi.org/10.35366/111508

incidence of 20 cases per million inhabitants.[2] It occurs most frequently between 50 and 60 years of age with no predominance of either sex. This tumor can affect any portion of the digestive tract, and its specific distribution corresponds to 70% gastric, 25% small intestine, 5% colon and rectum, and 2% esophageal.[3] While most gastrointestinal stromal tumors (GIST) are sporadic, there are reports of association with familial syndromes.[4] Their behavior can be benign or even metastatic during diagnosis. There are multiple options for diagnosis, such as computed tomography or magnetic resonance imaging; however, the gold standard is identifying the KIT protein (CD 117) in immunohistochemistry, present in this type of tumor in up to 60-70%. The standard treatment of a GIST without metastasis is complete surgical resection. In the advanced stages of the disease, targeted therapy with protein kinase inhibitors has improved the survival and management of this type of tumor and reduced its recurrence.

MATERIAL AND METHODS

A longitudinal, retrospective, observational, and clinical study was conducted in patients with histopathological diagnosis of GIST treated between January 2012 and December 2022 in the Oncology Unit of the General Hospital of Puebla. The information was obtained based on medical records, evolution notes, surgical records, histopathological reports, and immunohistochemistry tests.

The variables analyzed were incidence, the average age at diagnosis, most frequent symptoms, the diagnostic method used, location, mitotic index, immunohistochemistry, type of surgery performed, survival, and recurrence.

For data management, means between independent groups were recorded, and a parametric statistical test was applied. Categorical variables are reported in frequency and percentages.

RESULTS

Twenty-four files with a diagnosis of GIST confirmed by histopathology and immunohistochemistry were reviewed. During the study period, 1,169 patients diagnosed with gastrointestinal tract neoplasia were attended. The institutional incidence of GIST currently corresponds to 2%.

In the study period, the highest incidence was found in 2022, with five cases, 20.8% in relative terms, 16.6% of patients in 2018 and 2021 for each year, and 12.5% in 2016 and 2017. There was no record of cases in 2019, and in the remaining periods, there was only one diagnosed case *(Figure 1)*.

As a numerical variable, a descriptive statistical analysis was performed. The mean age at diagnosis was 53.2 years. The age range was from 35 years to 75 years at its upper limit. The most frequent age of presentation was 56 years, with five cases presented, which coincided with the statistical median and was also close to the average age. The standard deviation was 11.26 years. The second peak was 36 years, with four cases *(Figure 2)*.

Skewness and kurtosis were analyzed when trying to find a normal distribution behavior in the data because $n < 30$. In the case of the skewness coefficient, a value of -0.13 was obtained, which, although it tends to zero, being less than zero indicates a slight bias of the data to the right, while the kurtosis was -0.85, being negative, in which case the distribution was platykurtic.

A higher incidence was detected in the male sex, with 15 cases versus nine cases in the female sex.

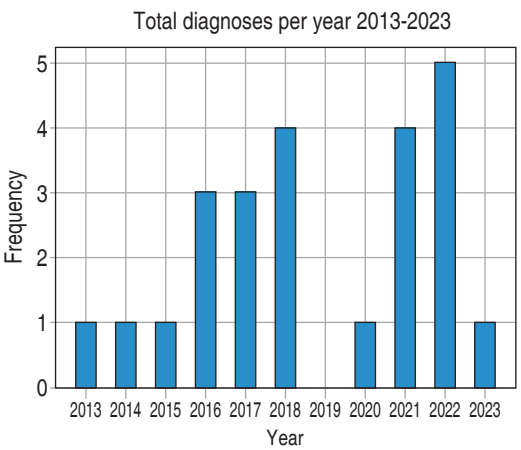

Figure 1: *Annual incidence during the study period.*

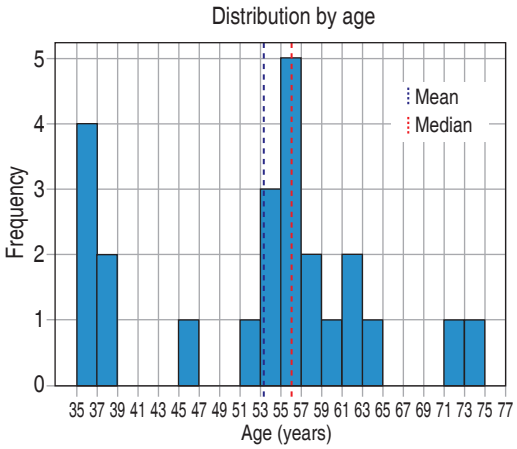

Figure 2: *Frequency and age at diagnosis.*

It was observed that 58% started with symptoms compatible with abdominal pain and weight loss; 25% began with an episode of intestinal occlusion in the emergency department. Only 12.5% presented data of lower gastrointestinal tract bleeding as the only clinical reference *(Figure 3)*.

Regarding the diagnostic method, histopathologic findings after surgical resection were more frequent in 45% of the cases. In the second place, the diagnosis was made by endoscopy in 33% of the patients. It was only identified as a tomographic finding in 20% of the cases.

The tumor location in this series was observed to be more significant in the small intestine, with 66%. Gastric GIST was present in 29% of the cases and the sigmoid colon in 4%, without manifesting in any other digestive tract region *(Figure 4)*.

The most frequent mitotic index in this series of cases was low (one to two in 50 fields) at 58%, while at 29%, a high mitotic index was found (> 5 in 20 areas). In turn, 8% showed no mitosis in the histopathologic study.

Immunohistochemistry revealed the presence of KIT protein (CD 117) in 100% of the cases studied; other markers such as CD34 were detected in 54% of the patients, while discovered on gastrointestinal stromal tumor 1 (DOG1) was only reported in 4% *(Table 1)*.

The patients received surgical treatment in 96% of the cases; 58% underwent intestinal resection of the tumor segment and entero-entero-terminal anastomosis. For gastric location, total gastrectomy with esophageal-jejunum anastomosis was performed. Of the patients, 4% did not seek treatment after diagnosis *(Figure 5)*.

Five-year survival was present in 16% of the cases. Of the patients, 41% are still being followed up. Survival of less than five years was observed in 41% of the patients.

There was recurrence in 16% of cases with tumor activity in the liver and lung.

DISCUSSION

Gastrointestinal stromal tumor (GIST) refers to mesenchymal tumors of the gastrointestinal

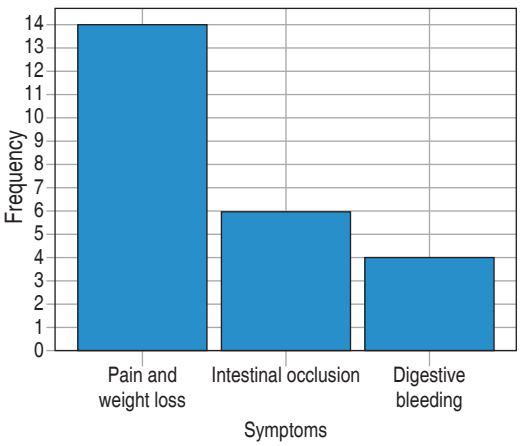

Figure 3: *Frequency of symptomatology presented.*

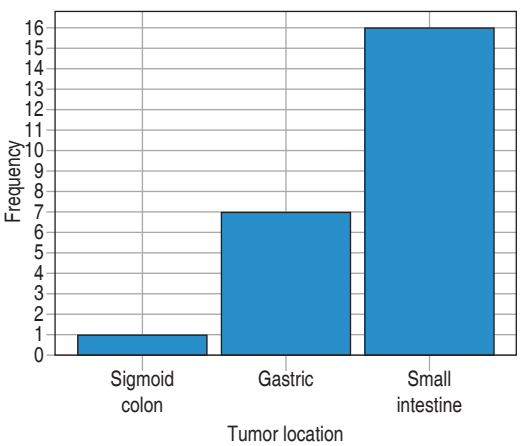

Figure 4: *Most frequent tumor location.*

tract originating from the interstitial cells of Cajal.

The cells of Cajal are a cell lineage of the intestinal stroma located between the longitudinal and circular muscle layers. They are related to the coordination and control of intestinal motility.[5] In GIST, the literature mentions an approximate incidence of 0.3-2% of gastrointestinal tumors,[6] of which corresponds to that found in the oncology unit. Although the literature describes a 1:1 female-to-male ratio, some studies suggest a higher tendency in the male sex.[7] Regarding this series, it was observed that most cases (66.6%) corresponded to men compared to 37.5% in the female sex. In absolute terms, the difference is not very significant since it barely reached a range of six cases per sex. Some studies reveal an equiprobable incidence; however, a greater tendency has been reported in the male sex.[8] According to the literature, the age of presentation ranges between 60 and 69 years,[9] and there are even reports of cases in children; however, in this review, the highest peak was found at 56 years, which corresponds to the average age (interval 35-75 years), despite this, the second peak at 36 years (16%) is under study.

GIST can appear in any part of the gastrointestinal tract, from the esophagus to the rectum, and there are even reports of extraintestinal locations such as the mesentery, omentum, or retroperitoneum. Despite its wide distribution, 50-60% occur in the stomach, 20-30% in the small intestine, 5% in the esophagus, and 5% in the rest of the abdominal cavity. Something worth mentioning in this series is that the highest incidence in its location is intestinal, with 66% in comparison with the gastric area found in 29% and its comparison with what is described in the literature. It is considered that even despite the size, mitotic index, and age of the patient, the location is an important prognostic factor since tumors originating in the small intestine, rectum, or mesentery are associated with a less favorable outcome than those arising in the stomach.[10]

Table 1: Immunohistochemical patterns.

Patients	Immunohistochemical pattern
13	CD 117 (+) CD34 (+), CK 20 (-)
9	CD 117 (+) CD34 (-), CK 20 (-)
1	CD 117 (+) DOG1 (+) CD34 (-) Cytokeratin (-)

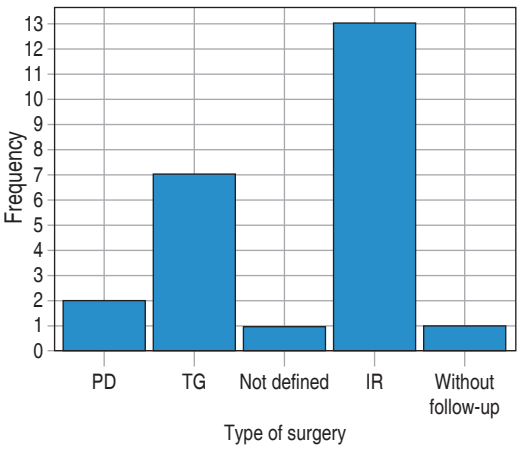

Figure 5: *Type of surgery performed and its frequency. IR = intestinal resection. TG = total gastrectomy. PD = partial duodenectomy.*

Regarding its clinical presentation, it is reported that a high percentage remains asymptomatic until it is observed as a finding at the time of a study. In symptomatic patients, the manifestations are usually non-specific and erratic and correspond to 70% of patients with this type of tumor.[11] Gastrointestinal tract bleeding is the most frequent symptom, followed by abdominal pain, weight loss, and a palpable mass. In this series, the most frequent symptom was non-specific abdominal pain and weight loss (58%), followed by episodes of intestinal occlusion (25%) and, finally, gastrointestinal tract bleeding (12.5%).

Histologically, GIST is described as a tissue consisting of cells with morphology described in one of three categories: spindle cells, epithelioid, and mixed type.[12] By the early 1990s, there was confusion regarding the lines of differentiation shown in this type of tumor; thanks to studies performed around mutations in the KIT protein and its expression, this field was transformed concerning tumor diagnosis.[13] KIT is a receptor tyrosine kinase type III. It presents its activation with stem cell factor binding with subsequent activation of

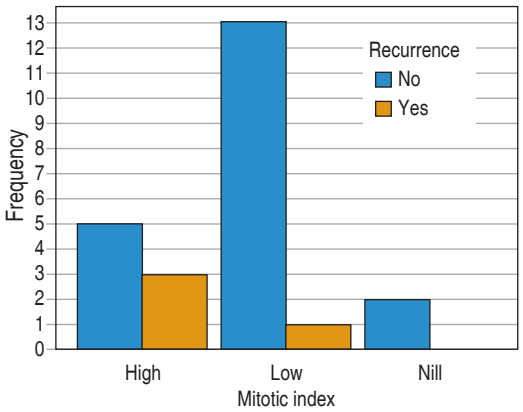

Figure 6: *Relationship between mitotic index and recurrence.*

signal transduction pathways resulting in cell proliferation, differentiation, maturation, and survival, showing its derivation from Cajal's interstitial cells.[14] Because of this, it was determined that a characteristic of GISTs is the expression of CD 117 (KIT) in 90-95% of cases, followed by CD34 in 60-70%. In this series, positivity for CD 117 was found in 100% of cases, followed by CD34 in 54% and only 4% for DOG1 *(Table 1)*.

Due to the no specificity of the clinical picture, approximately 50% of patients have metastases at the time of diagnosis. Diagnostic imaging methods include computed tomography scan, magnetic resonance imaging, PET scan (positron emission tomography), and ultrasound. Of these, tomography is the most useful and has the advantage of showing invasion and metastasis.[15] In this review, it was observed that 45% were histopathologically diagnosed after tumor resection, while 30% obtained a pre-surgical histopathological diagnosis by endoscopy and only 20% by tomographic findings.

GIST has an uncertain malignant potential. In conjunction with tumor diameter, the mitotic index has been used to stratify the risk of recurrence in this type of tumor. Reports indicate that a mitotic index higher than five mitoses/50 fields (high) has a recurrence risk of 86%.[9] At the same time, indexes lower than five mitoses/50 fields (low) are reported with a recurrence risk of 11%. This study found a low mitotic index of 58% and a high index of 29% *(Figure 6)*. The most common sites of recurrence are the liver (65%), peritoneum (50%), and both (20%). This study detected recurrence in 16%, with tumor activity in the liver and lung.[16] Of this group of patients, 75% presented a high mitotic index, while 25% showed a low mitotic index.

Treatment is dependent on size, location, and dissemination. Surgery is considered the initial treatment, which is the gold standard with complete resection in the early stages and a curative potential if negative margins are achieved.[17] Regional lymph node dissection is of little value due to the absence of metastases at this level. In the case of unresectable disease, which is reported in the United States between 13 and 50%,[18] or if there is a high risk of recurrence, the use of tyrosine kinase inhibitors (imatinib, sunitinib, regorafenib) is used as medical treatment. This type of drug is considered the standard treatment in metastatic disease.[19] It responds poorly to chemotherapy, while radiotherapy is only used for analgesic purposes or in case of intraperitoneal bleeding.

CONCLUSIONS

Gastrointestinal stromal tumors have unpredictable behavior. Due to the low relative frequency of GIST, it is essential to consider it among the diagnostic alternatives for abdominal tumors for the most suitable treatment possible. Although surgery is regarded as the curative treatment for this type of tumor, the risk of detecting it in advanced stages is high due to the insidiousness of the clinical presentation. Applying the KIT protein (CD 117) as a diagnostic marker and even as a therapeutic target using tyrosine kinase inhibitor drugs has improved survival in these patients.[20] Close long-term follow-up is essential because of the high risk of recurrence. Studies in more extensive series of GIST are required to clarify etiological and risk factors, as in this study in which the highest frequency was observed in the male gender or the presentation of the tumor was detected at an early age.

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Ethical considerations and responsibility: data privacy. According to the protocols established in our work center, we declare that we have followed the protocols on patient data privacy and preserved their anonymity.

Funding: no financial support was received for the preparation of this work.

Disclosure: none of the authors have a conflict of interest in the conduct of this study.

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