ORIGINAL ARTICLE

Gastrointestinal stromal tumors: experience of the digestive tract tumors and prognostic risk analysis cooperative group

Catherine Sarre-Lazcano¹, Erika Ruiz-García², Rafael Medrano-Guzmán³,
Daniel Motola-Kuba and Heriberto Medina-Franco^{1,*}

¹Staff physician, Surgery Head Office, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán; ²Department of Medical Oncology, Instituto Nacional de Cancerología; ³Department of Oncological Surgery, Centro Médico Nacional Siglo XXI, IMSS, Ciudad de México, Mexico

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KEY WORDS

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Risk stratification;
Recurrence;
Survival

Abstract Background: A cooperative group was conformed between the digestive tract tumor departments from the Centro Médico Nacional Siglo XXI, Hospital Médica Sur, Instituto Nacional de Cancerología and the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. **Objective:** To describe the institutional experience of the aforementioned centers in GIST (gastrointestinal stromal tumors) from 2000 to 2015 and analyze the prognostic factors. **Methods:** A retrospective, descriptive, analytic study was performed, registering demographic, clinic, surgical, pathological and follow-up data of patients with GIST diagnosis reported by each institution. Kaplan-Meier charts were constructed for the survival analysis, which were compared using the log-rank test, considering $p < 0.05$ as statistically significant. **Results:** A total of 274 cases were registered, with an even distribution between both sexes. The mean population age was 55 years, with the most frequent localization being the stomach (55,1%). Metastatic disease at diagnosis was found in 63 patients (28%). Mean size was 8.7 cm, with low-grade tumors being more frequent (36,5%). Mean follow-up was 42 months. Factors negatively associated with disease-free survival and overall survival were non-gastric localization, size > 5 cm, high-grade tumors (> 5 mitosis/field) and an intermediate or high recurrence risk. **Conclusions:** National experience is comparable to prognostic factors reported in international literature. Size was found to have a smaller impact in overall survival than tumoral grade. (creativecommons.org/licenses/by-nc-nd/4.0/).

*E-mail for correspondence: herimd@hotmail.com (H. Medina-Franco)

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INTRODUCTION

Background

Gastrointestinal (GI) tract stromal tumors (GIST) are the most common GI tract tumors, and account for < 1% of GI primary neoplasms. They occur more frequently in the 40-60-year age group, with a similar incidence in both genders. Most common localization is the stomach, followed by the small bowel, although they can affect any part of the GI tract¹.

GIST has an incidence of 20 cases per million per year, and a prevalence of 129 cases per million², although its frequency is thought to be underestimated, since most tumors are of less than 1 cm and can be asymptomatic³.

They originate in the cells of Cajal, which act as an intestinal pacemaker. These cells are intertwined with muscle cells' intramural neurons, and its loss has been associated with gastroenteric arrhythmias and diabetic gastropathy. Most cases are sporadic; however, up to 5% can be associated with dominant autosomal syndromes, such as the Carney-Stratakis syndrome, type 1 neurofibromatosis or familial GIST associated with mutations at c-KIT, which result in membrane receptors abnormal self-activation and an intracellular signaling cascade via tyrosine-kinase⁴.

Main treatment modality is complete surgical resection without rupture of the tumor pseudo-capsule, and neoadjuvant treatment with tyrosine-kinase inhibitors (TKI) has an important impact on patient survival for tumor size reduction or as adjuvant according to the risk of recurrence, calculated based on tumor size, grade and localization⁵.

OBJECTIVES

A cooperative group was formed between the GI tract tumors departments of the Centro Médico Nacional Siglo XXI, Médica Sur, Instituto Nacional de Cancerología and Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán hospitals, with the purpose to describe these centers' institutional experience on GIST from year 2005 to 2015 and to analyze disease-free survival (DFS) and overall survival (OS)-associated prognostic factors.

MATERIAL AND METHODS

A retrospective, descriptive, analytical study was carried out, where demographic, clinical, surgical, pathological and follow-up variables were recorded in GIST-diagnosed cases reported by each institution. Kaplan-Meier survival curves were plotted and compared with the log-rank test, with a p-value < 0.05 being considered significant.

RESULTS

General characteristics

A total of 274 cases were recorded: 89 from the Instituto Nacional de Cancerología (32.5%), 86 from the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (31.4%), 50

from the Centro Médico Nacional Siglo XXI (18.2%) and 49 from the Médica Sur Hospital (17.9%). Between-gender distribution was equitable, with 149 women (54.4%) and 125 men (45.6%). Mean age was 55 years (range: 11-89). There were 62 patients originating from Mexico City (22.6%), 12 from the State of Mexico (4.4%) and 53 from the rest of the Republic (19.3%), as well as 2 foreign patients (Panama and Dominican Republic); the place of origin was not recorded in 145 patients (52.9%).

Most common localization was the stomach, with 151 cases (55.1%), followed by the small intestine with 93 cases (33.9%), colon with 8 cases (2.9%), rectum with 8 cases (2.9%) and esophagus with 3 cases (1.1%), and there were 11 cases of retroperitoneal localization (4%). At diagnosis, 63 patients were found to have metastatic disease (23%).

With regard to laboratory data, mean hemoglobin was 11.7 g/dL, and 66 patients were found to have anemia at diagnosis (48.5%). Mean albumin was 3.7 g/dL, with 35 patients with hypoalbuminemia (26.3%).

Treatment

Neoadjuvant treatment with TKIs was administered in 5 cases (1.8%). Surgical treatment was documented in 133 cases, and the most common procedure was partial gastrectomy in 69 cases (51.9%) and total gastrectomy in 6 cases (4.5%), followed by small bowel resection in 38 patients (28.6%). Five patients (3.8%) underwent the Whipple procedure; 2 (1.5%), esophagectomy, and 2 (1.5%), colectomy. There was one case of endoscopic mucosectomy reported. Multi-organ resection was practiced in 21 patients (15.7%), and complete macroscopic resection in 76 (57.1%).

Complications were reported in 20 patients, with no data on their severity.

Pathology

Mean tumor size was 8.7 cm; there were 28 patients with tumors smaller than 2 cm (10.2%), 69 with tumors from 2 to 5 cm (25.2%), 78 with tumors from 5 to 10 cm (28.5%) and 78 with tumors larger than 10 cm (28.5%).

One-hundred cases corresponded to low-grade tumors (36.5%), defined as ≤ 5 mitoses per high-power field, and 54 cases corresponded to high-grade tumors (19.7%).

Only in 51 cases there was description of the histopathological pattern: 29 cases had spindle-cell pattern (56.9%), 11 cases had epithelioid pattern (21.6%) and 11 cases had mixed pattern (21.6%). The C-KIT mutation was recorded in 224 cases (81.8%).

Follow-up

The risk of recurrence was calculated according to tumor localization, size and grade, with 165 patients having the necessary data (60.2% of the sample). There were 6 patients with null risk (3.6%), 16 with very low risk (9.7%), 56 with low risk (33.9%), 26 with intermediate risk (15.8%) and 61 with high risk (37%).

Sixty-two patients received adjuvant therapy with TKIs (23%), with a mean treatment duration of 23 months (range: 1 to 96).

Recurrence was reported in 50 patients (18.2%), with a DFS mean of 33 months (range: 0-177).

Mean follow-up was 42 months (range: 0.1-323), with 216 patients alive (78.8%) and 33 deaths (12%), without the cause being specified. Twenty-five patients were lost to follow-up (9.1%).

Statistical analysis

Tumor characteristics and their association with DFS and OS were analyzed using Kaplan-Meier curves (Tables 1 and 2, respectively), and extra-gastric localization, tumor size larger than 5 cm, high tumor grade (> 5 mitoses/field) and intermediate or high recurrence risk were found to be significantly associated with both decreased DFS and decreased OS.

The relationship of anemia and hypoalbuminemia with DFS and OS was also analyzed, and it was not significant.

DISCUSSION

In this analysis we could observe that there are notable gaps between each institution's data bases, which is attributable

to the retrospective nature of this study and to a lack of homogenization of the characteristics included in the pathology reports, such as histological pattern and tumor grade, with the latter being of crucial importance for recurrence risk calculation and adjuvant treatment decision⁶. From this observation, the need to standardize inter-institutional databases in order to attain better registration of these neoplasms is deduced.

We found that GIST patients' clinical characteristics in the Mexican population are consistent with those described in the world literature with regard to demographic distribution and tumor localization⁷.

We observed that neoadjuvant treatment with TKIs was administered to a very small proportion of patients, which is not consistent with the significant proportion of tumors larger than 5 cm that was observed; currently, the treatment of choice for locally advanced GIST is neoadjuvance with imatinib in order to improve tumor resectability and to reduce the risk of recurrence⁸. This low proportion of patients treated in the neoadjuvant modality may be due to an absence of reports on the databases, high cost of the medication in the private setting, lack of access and to non-inclusion of the drug in the social security systems as neoadjuvant treatment.

Similarly, among the 87 patients with intermediate or high recurrence risk, adjuvant treatment with TKIs was found to be reported only in 37 (42.5%), which is an alarmingly low percentage, since imatinib adjuvant administration for 1-3 years in patients with intermediate or high recurrence risk has been described to increase DFS and OS^{9,10}.

In some patients, treatment duration was affected by intolerance to adverse effects, availability of the medication or by patient financial means, without disregarding the possibility of cases with adjuvant treatment that were not reported in the databases.

In the statistical analysis, factors associated with decreased DFS were observed to be similarly associated with decreased OS, which is consistent with worldwide reports¹¹, and size was found to confer less impact than tumor grade, both significantly. This is probably due to the fact that tumor grade is more closely related to tumor biology, whereas size is dependent on localization and on the symptoms it elicits.

Table 1. DFS-associated factors

Characteristic	Mean DFS (months)	p
Localization:		
- Esophagus	0 (recurrence in both cases)	
- Stomach		
- Small intestine		
- Colon		
- Rectum		
- Retroperitoneum		
Size:		
- ≤ 5 cm		
- > 5 cm		
Grade:		
- Low grade		
- High grade		
Recurrence risk:		
- Very low/low		
- Intermediate/high		

Table 2. OS-associated factors

Characteristic	Mean DFS (months)	p
Localization:		
- Esophagus	NA (there were no deaths)	
- Stomach		
- Small intestine		
- Colon		
- Rectum		
- Retroperitoneum		
Size:		
- ≤ 5 cm		
- > 5 cm		
Grade:		
- Low grade		
- High grade		
Recurrence risk:		
- Very low/low		
- Intermediate/high		

CONCLUSIONS

Decreased DFS and OS-associated prognostic factors reported in the literature are consistent with the national experience shown in this study. Tumor grade was shown to be a better negative marker for OS than tumor size. An institutional cooperation effort is required in order to standardize databases and thereby obtain information with higher statistical power.

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