

Surgical and histopathologic outcomes of gastrointestinal stromal tumors



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BACKGROUND: *Gastrointestinal stromal tumors are encountered more frequent as a result of increased imaging examinations. The purpose of the study is to define the patient profile, histopathologic and treatment outcomes of cases that underwent surgical treatment for neoplasms of the gastrointestinal tract and diagnosed as gastrointestinal stromal tumor.*
METHODS: *The outcomes of 32 patients operated in our department of general surgery for tumors of the gastrointestinal tract and diagnosed as gastrointestinal stromal tumor between January 2014 and December 2019 are evaluated retrospectively from the medical records and hospital treatment registry.*

RESULTS: *Within the study period a total of 32 patients were operated and diagnosed gastrointestinal stromal tumor. There were 19 male (59.4%) and 13 female (40.6) patients and the average age of the patients was 60.2±11.8 years. The average tumor size was 5.95±3.3 centimeters. The tumor localization was mainly the stomach (n=17) and the small bowel (n=11). Distant metastasis was detected in 6 (18.75%) patients, four of them in the liver and two in the peritoneum and omentum. In half of the cases (n=16) there were reactive lymph nodes and 5 (83.3%) of the metastatic patients were within them.*

CONCLUSION: *Gastrointestinal stromal tumors are more frequently encountered by the surgeons with the help of imaging techniques. The primary treatment is surgery and the results are promising. Patients with reactive lymph nodes should be examined for metastasis. Chemotherapy with imatinib can be used for inoperable patients. Patients should be followed up with computed tomography.*

KEY WORDS: Gastrointestinal System, Histopathology, Stromal Tumor, Surgery

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal (GI) tract such that 80-90% of mesenchymal tumors originating from the GI tract are GISTs. They account for 1% of all GI tumors. In the GI tract, they are mostly seen in the stomach. These are mesenchymal tumors

originating from the interstitial cells of Cajal which are pacemaker cells located in the myenteric plexus or from neoplastic transformation of these cells, and smooth muscle cells of the digestive tract^{1,2}. Previously, most of these tumors were known as leiomyoma or leiomyosarcoma. As a result of the developing immunohistochemical and cytological examinations, it has been understood that most of them are actually GISTs³. GISTs can be seen all over the GI tract. They are most commonly located in the stomach (50-65%), in the small bowel (20-30%), colon and rectum (10%) and esophagus (5%). To a lesser extent, they can be seen in the mesentery, peritoneum, omentum, liver, pancreas, uterus, ovaries and in membranes of the retroperitoneal organs^{4,5}. These tumors commonly metastasize to the liver and to the abdominal membranes (peritoneum, mesentery, and the omentum)^{4,6}. The disease affects both genders equally.

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It is most frequently diagnosed between the ages of 50 and 70 years and can rarely be seen under the age of 40. The disease can also be found as a component of some tumor syndromes, but this is very rare^{1,2} information in the diagnosis and staging of malignant gastric stromal tumors compared to other methods^{1,10}. Biopsy is not recommended in these tumors because of the possibility of tumor spreading. The margins of surgical resection can be determined by perioperative frozen pathology. Nevertheless, an immunohistochemical examination is required for definitive diagnosis^{1,11,12}. The aim of the study is to define the patient profile, presentation of the disease, histopathologic results and treatment outcomes of GIST patients operated in our hospital.

Methods

The study included 32 patients operated in our department of general surgery for tumors of the GI tract and diagnosed as GIST between January 2014 and December 2019. The demographic data and the clinical data including clinical presentation, imaging examinations, surgical findings and histopathology reports were evaluated retrospectively from the medical records and the hospital treatment registry.

This study was approved by the local Clinical Research Ethical Committee of the Research and Training Hospital in our city (Decision no: 773/2020).

STATISTICAL ANALYSIS

Statistical Package for Social Sciences 20.0 for Windows was used for the analysis of the data. The variables were checked for normal distribution. Since the data was not distributed normally, Mann-Whitney U and Kruskal-Wallis tests were used for analysis of continuous variables between the groups. The results were expressed as mean±SD (min-max), n and percent (%). The values of $p < 0.05$ were considered as statistically significant.

Results

A total of 32 patients were operated and diagnosed as GIST. There were 19 male (59.4%) and 13 female (40.6%) patients and the average age of the patients was 60.2 ± 11.8 (43-84) years. The mean age of male patients was 56.05 ± 8.38 (43-72) years, while the mean age of female patients was $66.31 \pm$ (45-84) years. Abdominal pain was the main symptom among the patients (71.88%). GI bleeding (25%) was less common and only 4 patients (12.5%) had symptoms or signs of obstruction. Demographic characteristics and the symptoms or signs of the patients are summarized in Table I.

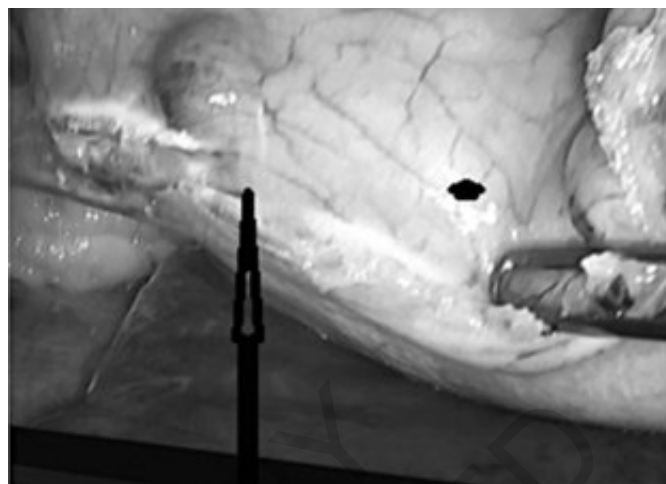


Fig. 1: Laparoscopic imaging of the tumor at the antrum in a sleeve gastrectomy patient.

The tumor localization was the stomach in 17 (53.12%) patients whereas 11 (34.38%) of them were located in the small bowel and 4 (12.5%) in the colon and rectum. The average diameter of the tumors was 5.95 ± 3.3 (1.5-20) centimeters. The diameter of the gastric tumors was 6.3 ± 4.3 (1.5-20), the diameter of the small bowel tumors was 5.64 ± 2.2 (3-9), and the diameter of the colorectal tumors was 5.67 ± 1.5 (4-7) centimeters. There was no statistically significant difference between the tumor size and the localization of the tumor ($p = 0.98$). Although regional lymphadenectomy is not recommended since GISTs seldom spread to lymph nodes, there were 16 cases with reactive lymph nodes detected by the pathologist in the surgical specimens. Three of the gastric tumors were diffusely metastasized to the liver, two of the small intestinal and one tumor of the colon were metastasized to the peritoneum and omentum. The data of tumor localization, size and lymphatic involvement or distant metastasis is summarized in Table II. Among the patients 24 of them underwent open surgery whereas laparoscopic surgery was performed in eight

TABLE I - Demographic and clinical characteristics of patients

	Number of patients (n)	Percentage (%)
Gender (M/F)	19/13	59.38/40.62
Age (Years) (Male)	56.05 ± 8.38 (43-72)	
(Female)	66.31 ± 13.76 (45-84)	
Symptoms:		
Abdominal pain	21	71.88
Dyspepsia	11	34.38
Weight loss	9	28.13
GI bleeding	8	25
Palpable mass	4	12.5
Obstruction	4	12.5

M/F: Male/Female, GI: Gastro Intestinal

patients and 6 of them were sleeve gastrectomy. The diameter of the tumors was less than 3.5 centimeters in patients who underwent sleeve gastrectomy (Fig. 1). In gastric tumors located at the fundus, total gastrectomy was performed, and subtotal gastrectomy was performed for tumors located at the antrum during open surgery. Segmental resection or subtotal resection was performed for the small bowel tumors. An abdominoperineal resection, a sigmoid colon resection and two subtotal colon resections were performed for the tumors located in colon or rectum. No intervention was performed for distant metastases of the patients with metastasized tumors.

Histopathological examination of the surgical specimens revealed necrosis in 22 cases, bleeding in 18 cases and ulceration in 8 cases. Vascular invasion was detected in one case. Although lymph node dissection was not per-

formed there were 16 (50%) specimens with reactive lymph nodes. Immunohistochemically, 31 patients had positive staining for CD117, and 27 patients had positive staining for CD34. Further analysis of the cases depending on presence of reactive lymph nodes is summarized in Table III.

The risk analysis scale created by Fletcher et al. is generally used to define the malignancy potential of GIST¹³. In terms of cell density, 14 patients had a low cell count, 10 patients had a moderate cell count, and 8 patients had a high cell count. As cell atypia, 18 patients had mild, 12 patients had moderate and 4 patients had severe atypia. In terms of mitosis, 24 patients had <5 mitosis/50 High Power Fields (HPF), 4 patients had 5-10/50 HPF, and 4 patients had >10/50 HPF. According to the Fletcher's risk classification 12 (37.50%) patients were in the very low-risk group, 10 (31.25%) were in the low-risk group, 5 (15.62%) were in the moderate-risk group, and the remaining 5 patients (15.62%) were in the high-risk group (Table IV).

Two of our patients with metastasis died due to cardiopulmonary causes in the early postoperative period. One of our patients with liver metastasis died 34 months and another patient with peritoneal involvement died 38 months after the operation. The other 2 patients are alive 18 and 22 months after surgery. Adjuvant chemotherapy was scheduled for 4 patients with metastasis and for 4 other patients in the high and moderate risk groups. The average follow-up period was 32.95±14.28 months. Unless necessary, we performed only oral and intravenous contrast-enhanced abdominal CT in the follow-up of the patients. None of our patients developed recurrence during the follow-up period.

TABLE II - Data of the tumor with respect to localization

	Stomach (n=17)	Small bowel (n=11)	Colon-rectum (n=4)	p
Percentage (%)	53.12	34.38	12.5	
Size (cm)	6.3±4.3 (1.5-20)	5.64±2.2 (3-9)	5.67±1.5 (4-7)	0.98
Lymph node (+/-) (n)	10/7	4/7	2/2	
Metastasis (+/-) (n)	3/14	2/9	1/3	

cm: centimeters

TABLE III - Clinical and histopathological data based on presence of reactive lymph nodes

	Reactive Lymph Nodes (n=16)	No Lymph Nodes (n=16)	p
Gender (M/F)	11/5	8/8	
Age (years)	56.3±10.0 (43-74)	64.1±12.5 (43-84)	0.086
Tumor size (cm)	7.69±3.6 (4-20)	4.22±1.7 (1.5-8)	0.001
Metastasis (+/-)	5/11	1/15	0.001
Ki 67 index (%)	11.5±12.9 (1-45)	5.06±7.4 (1-30)	0.026
CD 117 (+/-)	16/0	15/1	
CD 34	13/3	14/2	
SMA	9/7	8/8	
S 100	3/13	2/14	
Desmin	2/14	1/15	

M/F: Male/Female, cm: centimeters

TABLE IV - Risk analysis of the cases according to Fletcher's classification

	Stomach (n=17)	Small bowel (n=11)	Colon-rectum (n=4)	Total (n)	(%)
Very low risk	6	5	1	12	37.5
Low risk	6	3	1	10	31.25
Moderate risk	2	2	1	5	15.62
High risk	3	1	1	5	15.62

Discussion

GISTs are the most common mesenchymal tumors of the GI tract. Preoperative diagnosis is difficult and the diagnosis is often made at the time of surgery and thereafter with histopathological examination. Although they constitute a small number among GI cancers (0.1%-3%) the clinical course is favorable with complete resection of the tumor compared with other GI cancers which makes the diagnosis and treatment important^{1,2,4,14}.

These tumors are most commonly seen in the sixth decade of life and they affect both genders almost equally. In the GI tract, they are mostly located in the stomach and with a decreasing order in the small bowel, colon and rectum, and the esophagus^{4,6,7,14,15}. The mean age of the patients in our series was similar; on the other hand, the ratio of male gender was slightly higher. Also, gastric stromal tumors were the majority of our cases. Although we cannot comment whether or not they were stromal tumors, patients with tumors located in the esophagus were referred to a tertiary hospital. Therefore, we did not have any case with stromal tumors located

in the esophagus. GISTs are usually sporadic but rarely, they can present with some familial syndromes¹⁶. In our study, we did not have any familial GIST case.

In general GISTs less than 2 cm are asymptomatic and these tumors are incidentally identified during radiological and endoscopic examinations or surgeries. The symptoms and signs vary according to the location and size of the tumor. In our study the most common symptoms were abdominal pain, dyspepsia and weight loss. Bleeding usually develops due to mucosal ulceration and in 25% of our cases there was GI bleeding and two of them being operated urgently. Palpable mass was a rare finding among our patients with 4 cases.

There is no standard diagnostic method for GISTs. Contrast-enhanced CT is the most commonly used diagnostic method however endoscopic US can provide better information on localization, tumor size and depth. Definitive diagnosis of GISTs is made by biopsy as in other tumors. A biopsy can also be performed with endoscopic US but is necessary to be cautious, as there is a risk of bleeding since these tumors are hyper vascular and the tumor can spread to surrounding organs^{17,18}. The diagnoses of the cases were made with CT and US before surgery in our study.

The most effective treatment method is surgery and resection of the tumor including a negative surgical margin of 1 cm along with its pseudo capsule is sufficient^{4,15,17,19}. Laparoscopic surgery or endoscopic resection is also performed for these tumors and successful results are achieved^{10,20}. We also performed laparoscopic sleeve gastrectomy in six of our patients without any problem and open surgery was the choice for the rest. The average diameter of the tumors was 5.95 ± 3.3 centimeters ranging from 1.5 to 20 in our cases. The more extensive resection for the tumors in our cases was mainly due to lack of histopathologic diagnosis before surgery.

The risk analysis scale defined by Fletcher et al. is generally used to assess the malignancy potential of GISTs¹³. In our study all the patients in the high-risk group and one patient from the moderate-risk group had distant metastasis. There were 10 patients in these 2 groups. Two of our patients with metastasis died in the early postoperative period and so that adjuvant chemotherapy was scheduled for 4 patients with metastasis and for 4 other patients in the high and moderate risk groups. Immuno-histochemical studies of the specimens revealed 96.9% (n=31) positive staining for CD117 and 84.4% (n=27) positive staining for CD34. These rates were consistent with the literature^{3,7,9,17}. In half of our cases reactive lymph nodes were detected. The tumor size and Ki 67 proliferation index was higher in the group with reactive lymph nodes and the differences were statistically significant. Besides 83.3% (n=5) of the metastatic patients were within them. Also 90% of patients in the high and moderate risk groups were with reactive lymph nodes.

Chemotherapy should be considered for patients with

diffuse metastasis or who cannot undergo total excision and cannot be operated for other reasons. Imatinib is a tyrosine kinase inhibitor and is used in metastatic or unresectable GIST patients with positive staining for CD117. Imatinib is also used after surgical resection in high risk patients (according to Fletcher's classification) with a success rate of 50%-80% in remission and regression²¹. We also used imatinib in our metastatic patients with high tolerability. We suggest the use of imatinib in high and moderate risk patients with reactive lymph nodes.

Conclusion

GISTs are frequently seen in advanced ages and equally in men and women. The most common location is the stomach. In eligible patients, surgical treatment is the gold standard and it is important that the surgical margins are clear. The localization, size and histopathological necrosis of the tumor and the number of mitosis are the important factors in terms of prognosis. In patients with metastasis and recurrence or who are not eligible for surgical resection, imatinib is the most commonly used chemotherapeutic agent. We suggest the use of imatinib in high and moderate risk patients with reactive lymph node. Patients should be followed up with CT.

Riassunto

I tumori stromali gastrointestinali si incontrano più frequentemente come conseguenza del maggior numero di diagnostica per immagini. Lo scopo di questo studio è di definire il profilo del paziente, gli esiti istopatologici e terapeutici dei casi sottoposti a trattamento chirurgico per neoplasie gastroenteriche diagnosticate come tumore stromale gastrointestinale. Si tratta di uno studio retrospettivo eseguito sugli esiti di 32 pazienti di questo tipo operati nel nostro dipartimento di chirurgia generale tra gennaio 2014 e dicembre 2019 sono valutati retrospettivamente dalle cartelle cliniche e dal registro delle cure ospedaliere.

Sul totale dei 32 pazienti, 19 erano uomini (59,4%) e 13 donne (40,6); l'età media dei pazienti era di $60,2 \pm 11,8$ anni. La dimensione media del tumore era di $5,95 \pm 3,3$ centimetri. La localizzazione del tumore era principalmente lo stomaco (n = 17) e l'intestino tenue (n = 11). Metastasi a distanza sono state rilevate in 6 (18,75%) pazienti, quattro dei quali nel fegato e due nel peritoneo e nell'omento. Nella metà dei casi (n = 16) c'erano linfonodi reattivi e 5 (83,3%) dei pazienti metastatici erano al loro interno. Vengono brevemente segnalati gli esiti a distanza.

CONCLUSIONE: I tumori stromali gastrointestinali sono più frequentemente incontrati dai chirurghi con l'aiuto di tecniche di imaging. Il trattamento primario è la

chirurgia e i risultati sono promettenti. I pazienti con linfonodi reattivi devono essere esaminati per la metastasi. La chemioterapia con imatinib può essere utilizzata per pazienti inoperabili. I pazienti devono essere indagati nel follow-up con tomografia computerizzata.

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