Int Surg 2017;**102:**440–445
DOI: 10.9738/INTSURG-D-17-00076.1

Importance of Early Diagnosis of Gastrointestinal Stromal Tumors of the Stomach: Our 5-Year, Single-Center Experience

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Objective: The aim of this study was to investigate clinicopathologic characteristics, diagnosis, treatment, and prognosis of patients who underwent surgery with a diagnosis of a gastrointestinal stromal tumor (GIST) of the stomach.

Methods: In this single center study, the data of a total of 42 patients diagnosed with a GIST of the stomach in our center between 2010 and 2015 were retrospectively analyzed. The mean age was 60.6 years, with a male-to-female ratio of 1.47/1. Patients presented with various complaints (21 patients had stomach pain,14 patients were asymptomatic, 3 patients had hemorrhage, 2 patients had heartburn and acidity,1 patient had intumescence,1 patient had nausea and vomiting), and all patients underwent surgery. The initial diagnosis was made with endoscopy in 19 patients, with computed tomography in 21 patients, and with magnetic resonance imaging in 2 patients. Local excision or wedge resection was performed in 27 patients, whereas subtotal gastrectomy was performed in 15 patients.

Results: The mean tumor diameter was 5.66 cm. Pathologically, 25 patients had very low, 5 patients had low, 6 patients had moderate, and 6 patients had high-grade malignancy. The patients with moderate- to high-grade malignancy received imatinib. Liver metastasis occurred in 2 patients. The mean follow-up was 33 months. The mean disease-free survival time was 31.72 months, and the mean disease-specific ($n = 2$) survival time was 31.25 months. All patients including metastatic ones were still alive.

Conclusions: Our study results show that frequent use of imaging studies and increased use of endoscopic scans for various reasons may increase the rate of incidentally detected

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gastric stromal tumors. High rates of disease-free survival can be achieved in GIST patients who are in the low-risk group due to the early diagnosis.

Key words: Gastrointestinal stromal tumor – Incidental – Prognosis – Stomach

Although gastrointestinal stromal tumors (GISTs) account for less than 1% of gastrointestinal (GI) tumors, they are the most common mesenchymal tumors of the GI tract.[1] They mostly originate from the submucosa, muscularis mucosa, and serosa and are strictly limited to the mucosa.[2] These tumors are most frequently located at the stomach (55%–60%).[3]

A gastric GIST may present itself with stomach pain, hemorrhage, dyspepsia, nausea, mass palpation, or obstructive hepatitis. However, many patients are asymptomatic and are incidentally diagnosed through endoscopy or diagnostic imaging methods.[4] Standard treatment of localized gastric GIST is surgical resection with minimally invasive or open techniques, where negative margin is attained with intact tumor capsule. Wedge or full-thickness partial gastrectomy is the most effective treatment strategy for tumors localized at the stomach along the greater or lesser curvature.[5] On the other hand, anatomic gastrectomy (subtotal or total gastrectomy) can be performed for the tumors that take up a significant portion of the stomach. As lymph node metastasis is extremely rare, lymph node dissection is not routinely recommended.[5]

There are several large-scale studies on the prognosis and clinical characteristics of surgically treated gastric GISTs. With the aim of contributing to the current literature, in the present study, we aimed to investigate clinicopathologic characteristics, diagnosis, treatment, and prognosis of the patients who underwent curative surgical resection for primary gastric with a diagnosis of a GIST of the stomach.

Methods

A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

This retrospective, single center study included a total of 42 patients with a GIST of the stomach who underwent curative resection in Haydarpasa Numune Training and Research Hospital between January 2010 and December 2015. Inclusion criteria were as follows: the presence of a GIST of the stomach confirmed by the pathologic evaluation in our center. Data including age and sex of the patient, clinical presentation, results of the preoperative diagnostic methods, selection of the surgical method, histopathologic evaluation, disease-specific and disease-free survival, adjuvant treatment, and recurrence were recorded.

Statistical analysis

Statistical analysis was conducted by using the Statistical Package for the Social Sciences 16 (SPSS Inc, Chicago, Illinois). Descriptive data were expressed in mean and SD for quantitative variables and in frequency and percent for qualitative variables.

Results

Clinical findings

The mean age was 60.6 (range, 37–83) years, with a male-to-female ratio of 1.47/1 (25 males, 17 females). The primary complaint was epigastric painin in 21 patients (50%). A total of 14 patients (33.3%) were asymptomatic, and their tumors were incidentally detected. Three patients (7.1%) were admitted with gastrointestinal hemorrhage. Other complaints included heartburn and acidity (n = 2), intumescence (n = 1), and nausea and vomiting (n = 1).Clinical data of the patients are summarized in Table 1.

Initial evaluation

For the initial evaluation, endoscopy was performed in 19 patients (45.2%). None of the patients had mucosal ulceration, and endoscopic biopsy was not performed. In 1 patient with nausea and vomiting, it was found that the tumor caused gastroduodenal intussusception. Endoscopic ultrasonography was performed in 4 patients, and biopsy was not required.

Contrast-enhanced computed tomography (CT) was performed in 21 patients (50.0%), and magnetic resonance imaging (MRI) was performed in 2 patients (4.8%). Tumor growth patterns varied and exogastric (n = 12), endoluminal (n = 7), and intramural (n = 4) growth were observed. Tumor

Table 1 Clinical characteristics of patients with gastric GISTs

Characteristics	Parameters
Age, y	
≤60	18 (42.9%)
>60	24 (57.1%)
Sex	
Male	25 (59.5%)
Female	17 (40.5%)
Clinical presentation	
Abdominal pain	21 (50.0%)
Asymptomatic	14 (33.3%)
Hemorrhage	3 (7.1%)
Other	4 (9.6%)
Diagnosis	
Endoscopy	19 (45.2%)
CT	21 (50.0%)
MRI	2 (4.8%)
Surgical procedure	
Wedge resection	27 (64.3%)
Subtotal gastrectomy	15 (35.7%)
Adjuvant therapy (imatinib)	
Yes	12 (28.6%)
No	30 (71.4%)

Table 2 Pathologic characteristics of patients with gastric GISTs

Characteristics	Parameters
Tumor size, cm	
≤2	3 (7.2%)
2.1–5	24 (57.1%)
5.1–10	11 (26.2%)
>10	4 (9.5%)
Histologic type	
Spindle	25 (59.5%)
Epitheliod	6 (14.3%)
Mixed	11 (26.2%)
Mitotic index	
≤5	33 (78.6%)
>5	9 (21.4%)
Immunohistochemisty	
CD117 (+++, ++ positive)	40 (95.2%)
CD34 (+++ positive)	37 (88.1%)
(+ positive)	1 (2.4%)
S100 (+ positive)	3 (7.1%)
NIH risk category	
Very low risk	25 (59.5%)
Low risk	5 (11.9%)
Intermediate risk	6 (14.3%)
High risk	6 (14.3%)

markers were analyzed in all patients, and all were negative. Pathologic diagnosis confirmed the initial diagnosis in all patients (100%).

Pathologic and immunohistochemical findings

The mean diameter of the tumors was 5.66 cm (range, 1–19 cm). Based on the histopathologic findings (tumor size and mitotic rate), 6 patients (14.3%) had high-grade, 6 patients (14.3%) had moderate-grade, 5 patients (11.9%) had low-grade, and 25 patients (59.5%) had very low-grade malignancy. Histologically, 25 patients had spindle, 11 patients had mixed, and 6 patients had epithelioid-type morphology. None of the lymph node specimens had metastasis. Of the specimens obtained from all patients, 40 (95.2%) showed a strong CD117 positivity with the immunohistochemical staining. In addition, weak positivity was observed in 2 patients (4.8%). A total of 37 patients (88.1%) were strongly positive for CD34, whereas 3 patients (7.1%) were weakly positive and 2 patients were negative. Only 1 patient was positive for SMA, and 3 patients were weakly positive for S100 (Table 2).

Surgical procedure and follow-up

All patients underwent open surgery. Local excision or wedge resection was performed in 27 patients (64.3%), whereas subtotal gastrectomy was performed in 15 patients (35.7%). None of the patients had surgical margin positivity, and in-hospital mortality was not observed. Based on the histopathologic findings, there were 6 patients with high-grade malignancy, whereas 6 patients had moderate-grade malignancy. According to these findings, a total of 12 patients received imatinib treatment.

The mean follow-up was 33 (range, 5–58) months. Although a CT scan was performed once a year in low-risk patients, intermediate- and high-risk patients underwent CT every 3–6 months. All patients underwent gastroscopy once a year for the first 2 years (Table 3). Liver metastasis was detected in the early postoperative period in 2 high-grade patients (4.5 and 7 months, respectively). The mean disease-free survival time was 31.72 (range, 4.5–58) months, whereas the mean disease-specific (n = 2) survival time was 31.25 (range, 21–41.5) months. All patients including metastatic ones were still alive.

Discussion

GISTs were first described in 1998 on the identification of a *KIT* mutation in many patients by Hirota *et al*.[6] Its annual incidence in Western countries is ~7–14 cases per million.[7] The mean age at the time of diagnosis is 63 years with a slight male predominance.[7] However, these tumors can affect all age groups with a varying incidence depending on the race and country. Consistent with the literature, the

Table 3 Survival data of patients with gastric GISTs

Survival characteristics	Parameters
Follow-up, mo	
Mean (mean ± SD)	33.21 ± 14.27
Median (range)	26 (5–58)
Recurrence or metastasis	2
Mortality	0
Survival, mo	
Disease-free survival	31.72 ± 15.28 (4.5–58)
Diseased survival	31.25 ± 14.49 (21–41.5)

mean age was 60.6 years in our study, and there was a slight male predominance.[7,8]

Based on the results of a study including a total of 9747 patients diagnosed with a GIST, 81.3% patients were symptomatic, whereas 18.7% were asymptomatic.[9] Symptoms depended on the location, size, and aggressive behavior of the tumor. In our study, 33.3% of the tumors were detected incidentally, indicating a higher rate than those indicated in the literature. This suggests that more incidental and smaller GIST can be identified in health screening programs for various reasons.

Several methods such as CT, MRI, and upper gastrointestinal endoscopy are used in the diagnosis of GIST. In particular, contrast-enhanced CT is useful to characterize the lesion and to evaluate the severity of the disease and metastases. It can be also used during follow-up.[10] The GIST diagnosis can be made particularly using fine-needle aspiration biopsy (FNAB) from the submucosal lesions located at the upper gastrointestinal system via endoscopic ultrasonography.[11] In 95.2% of our patients, diagnosis was made via endoscopic examination and CT. No preoperative diagnostic biopsies were required in patients with a suspected GIST.

Surgical treatment is the first choice in localized and resectable GIST. Complete resection must be performed without disrupting the pseudocapsule to prevent tumor rupture and seeding. Lymph node metastasis is very rare at the time of diagnosis, and therefore, lymph node dissection is not routinely recommended.[5,12] Complete resection was performed in all our patients. None of the lymph node specimens had metastasis.

Primary GIST evaluation is performed based on 3 criteria (mitotic index, tumor size, and localization) recommended by the National Institutes of Health (NIH).[4,13] In the modified NIH classification by Joensuu,[14] tumor rupture was added. Modified NIH criteria can be a guide to identify patients who require adjuvant treatment. A study from Japan showed that modified NIH criteria were more sensitive in predicting the recurrence rates of patients.[15] According to the NIH GIST criteria, 15% of the tumors are in the very-low-risk, 30% are in the low-risk, 22% are in the intermediate-risk, and 33% are in the high-risk group.[9] In our study, 71.4% of the patients were in the very-low- and low-risk groups. These results indicate that as the GIST of the stomach detected in asymptomatic patients increase, the number of low-risk patients would also increase.

The most common marker in the diagnosis of GISTs is CD117 antigen. Approximately 97% of the GIST patients are positive for CD117.[16] However, the antigen is not specific to GIST. Some of the mesenchymal, neural, and neuroendocrine tumors can also react weakly with CD117.[13,16] In the present study, CD117, CD34, SMA, and S100 markers were positive in 100%, 95.2%, 2.4%, and 7.1% of our patients, respectively.

Adjuvant imatinib treatment following the complete resection of primary GIST was shown to decrease the recurrence.[17,18] Surgery was performed due to high-risk GIST in the Scandinavian Sarcoma Group (SSG) XVIII/AIO phase 3 trial, and the patients who subsequently received adjuvant imatinib treatment for 12 and 36 months were compared. Disease-free survival time was longer and recurrence rates were lower in the patient group who received imatinib treatment for 36 months.[18] Hence, adjuvant imatinib treatment was recommended to be continued for 3 years in high-risk GIST patients. However, there are no studies including the intermediate-risk group. The modified NIH criteria can be used to identify the candidate patients for imatinib treatment, as the SSG XVIII/AIO trial previously used these criteria in identifying the estimated GIST recurrence risks.[18] In our study, imatinib treatment was started in 12 patients (28.6%) and continued for 1 year in those who were in the moderate-risk group and for 3 years in those who were in the high-risk group.

Approximately 20%–25% of the gastric GIST and 40%–50% of the intestinal GIST have a clinically aggressive course, and metastatic spread is seen in about 10%–25% of these patients.[16,19,20] In a retrospective study, GIST were shown to metastasize usually to the liver and rarely to the lungs, bones, and brain.[13,20] In our study, only 14.3% of the patients were in the high-risk group and, of these patients, 2 (4.8%) had early liver metastasis. No recurrence or metastasis was detected during the follow-up in patients who were in the very-low-,

low-, and moderate-risk groups. These results suggest that the patients had a lower metastasis rate than those reported in previous studies. This can be attributed to the merit of early diagnosis and complete resection in asymptomatic patients.

In a retrospective study, 5-year survival rate in 80 patients who underwent complete resection due to a primary GIST and were using a tyrosine kinase inhibitor was 54%, and the mean survival time was 19 months in metastatic patients.[20] For the follow-up of the patients who underwent curative resection for recurrence or metastasis, CT scan was performed annually in low-risk group patients and every 3–6 months in the intermediate- and high-risk group patients. In our study, the mean follow-up was 33 months, and all patients were alive. In addition, the mean disease-free survival time was 31.72 months, and the mean disease-specific survival time of the 2 patients was 31.25 months. These rates are higher than the survival times reported in the literature. This can be attributed to the ambiguous biological behavior of the GIST and its wide phenotypic polymorphisms ranging from benign to malignant.

The limitations of the present study are its retrospective design and our limited experience of laparoscopic surgery in low-risk patients.

Conclusion

In conclusion, frequent use of imaging studies in Turkey, and increased use of endoscopic scans particularly for patients older than 40 years increase the rate of incidentally detected gastric stromal tumors. High rates of disease-free survival can be attained without using tyrosine kinase inhibitors in many gastric stromal tumor patients in the low-risk group with early diagnosis.

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