TURKISH JOURNAL of ONCOLOGY

Turk J Oncol 2017;32(1):19-24
doi: 10.5505/tjo.2017.1523

ORIGINAL ARTICLE

Gastrointestinal Stromal Tumors: A Single Center Experience

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OBJECTIVE

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumor of the gastrointestinal (GI) tract. The aim of this retrospective study was to explore the characteristics, prognostic factors, and treatment results of GIST cases.

METHODS

Clinical and pathological data of 35 GIST patients at our center between 2002 and 2015 were reviewed.

RESULTS

Total of 18 (51.4%) were women and 17 (48.6%) were men, with median age of 54 years. Common site of tumor was stomach (48.6%). Abdominal pain (37.1%) was common clinical symptom. Risk group distribution was 8.6% low, 31.4% intermediate, and 60% high-risk cases. Mean follow-up period of the patients was 34 months. Low-risk GIST can be treated with surgery alone. Recurrence was observed in only 1 of 10 patients who received adjuvant treatment. All 6 patients in whom metastasis was determined were in high-risk group, and 4 of them had liver metastasis. Metastasis was not detected in any of the patients who had <5 mitoses per 50 high-power field (HPF), but in 5 of 12 patients who had >10 mitoses per 50 HPF, metastasis was determined. Metastasis did not correlate with site or size of tumor, but was related to high mitotic rate (p=0.015). Median overall survival of the patients was 79 months.

CONCLUSION

Low-risk GIST can be treated with surgery alone. Imatinib therapy significantly improves survival of high-risk or advanced-stage GIST patients. Metastasis did not correlate with site or size of tumor, but correlation with high mitotic rate was observed.

Keywords: Gastrointestinal stromal tumors; prognosis; survival; treatment.

Introduction

Gastrointestinal stromal tumors (GISTs) are mesenchymal tumors localized in GI tract that supposed to be originated from intestinal pace maker cells normally found in intestinal wall (interstitial Kajal cells) or neoplastic formation of precursors of these cells.[1] Many tumors called as leiomyoma or leiomyosarcoma in previous years actually are thought be GIST.[2] C-Kit gene protein that regulates intracellular events is present in Cajal cells. Mutation in C-Kit proto-oncogene is important in pathogenesis of GIST. After autonomously activation of C-Kit receptor internal tyrosine kinase is activated. Consequently cell growth is stimulated and/or apoptosis is inhibited. Immune marker of C-Kit is CD117. C-Kit mutation is determined in

Received: January 29, 2017
Accepted: March 15, 2017
Online: March 20, 2017

Accessible online at:
www.onkder.org

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Turk J Oncol 2017;32(1):19-24
doi: 10.5505/tjo.2017.1523

85–90% of GISTs. In a significantly lower group (5% of cases), mutation of another tyrosine kinase proto-oncogene Platelet Derivated Growth Factor Receptor Alpha (PDGFRa) is present. In some of the GIST cases (<10%) no mutations can be detected.[3–5]

Annual incidence of GISTs is reported as 6–15/1,000,000.[6] It can arise from any part of GI tract from esophagus to anus. It is located most frequently in stomach (50–60%), and less frequently in small intestine (20–30%), esophagus (5%), and colon-rectum (10%). It can be seen rarely in intra-abdominal organ membranes such as omentum, peritoneum, mesentery, liver, pancreas, and uterus.[7] GIST patients most frequently admit to hospital with abdominal pain, symptoms and complaints of GI bleeding, obstruction or perforation. Some cases are asymptomatic and diagnosed because of other reasons.[2]

Surgery is the only curative treatment option in resectable cases. But even after complete resection recurrence occurs nearly in 40% of cases.[8] C-Kit receptor tyrosine kinase inhibitor imatinib is significantly improved median overall survival in situations such as surgically unresectable recurrence, metastatic disease or general condition is not proper for surgery and also in adjuvant treatment of high risk disease.[9] Neo-adjuvant treatment with imatinib allows less risky surgical procedures.[10]

Theoretically it is considered that all GISTs have malignity potential. For this reason risk determinations such as very low risk, low risk, intermediate risk and high risk are used in establishing the benefit of adjuvant treatment after curative surgery instead of benign or malign distinguishing. The most important prognostic factors in risk determination are tumor diameter and mitotic ratio. In 2002 Fletcher et al. made risk classification using tumor diameter and mitosis ratio.[11] According to Armed Forces Institute of Pathology Criteria (AFIP) published later, it is reported that tumor localization has also a prognostic role.[12] Finally in classification that Joensuu done, perforation of tumor determined as another prognostic factor increasing recurrence risk additionally to these factors.[13]

In this study we aimed to analyze demographical, pathological, and clinical features with prognostic factors and treatment results of our GIST cases seen rarely.

Materials and Methods

35 GIST cases admitted to our department of medical oncology and diagnosed between July 2002 and December 2015 were evaluated retrospectively. Files in hospital archive and department of oncology were scanned to obtain data of patients. Age at diagnosis, gender, date of diagnosis, diagnosis type, tumor localization of the patients were recorded. GISTs were determined histologically as spindle type, epithelioid type, and mixed type. CD117, CD34, smooth muscle actin, desmin, S-100 protein positivity as immunohistochemical markers and mitosis number in 50 high-power field were recorded. Tumor diameter is classified with largest diameter of primary tumor as <2 cm, <5 cm, 5–10 cm or >10 cm. Risk classification of the cases was done according to Joensuu's modified National Institute of Health (NIH) risk classification system.[14] According to this patients were grouped as very low risk, low risk, intermediate risk, and high risk. Pathology reports of patients who undergone surgery were examined in terms of microscopical disease presence in surgical margins. Patients who were metastatic at diagnosis were recorded. Treatments administered to patients, treatment responses, treatment related toxicities, and follow-up times were recorded from patient files and hospital automation system. Last situation of the patients were updated via death notification system or phone call. Consent from the university school of medicine ethical committee was received prior to the study, with regard to collecting, evaluating, analyzing, and interpreting the data.

Statistical analysis

All data obtained were recorded to Excel 2010 Microsoft program. SPSS (Statistical Package for Social Sciences) 17.0 statistics program was used for statistical evaluation and analyzes. Kaplan-Meier test was used for survival analyzes and Log-Rank analyze for comparisons. In survival analyzes, beginning date was taken as diagnosis date, last control date was taken as last control date for alive patients and exitus date for patients who were dead.

Results

Of the total 35 patients 18 (51.4%) were female, 17 (48.6%) were male, and median age was 54 (36–81). Anatomical localizations were GIS in 29 (82.9%), and extra-GIS in 6 (17.7%) cases. 48.6% (n=17) were localized in stomach, 31.4% (n=11) in small intestines, and 2.9% (n=1) in colorectal region. 17.1% (n=6) of the cases were originated from other intra-abdominal regions or retro-peritoneum. The most common complaint was abdominal pain (37.1%), second most com-

mon was bleeding (25.7%), and third most common was nonspecific symptoms due to abdominal mass (17.1%). Acute abdomen was present in two cases. 13 (37.1%) patients were diagnosed with endoscopic biopsy, 20 (57.1%) patients with surgery, and 2 (5.7%) patients with tru-cut biopsy. Tumor diameter at diagnosis was mostly (45.7%) between 5–10 cm. In 31.4% patients tumor diameter was over 10 cm. According to Joensuu's modified NIH risk classification system that takes account mitotic index and primary tumor diameter, 8.6% of the patients were in low risk group, 31.4% in intermediate risk group, and 60% were in high risk group. 6 (17.1%) patients had metastatic disease at diagnosis. Metastasis localizations were liver (4 cases) and peritoneum (2 cases). In two cases liver metastasis were occurred in follow-up after surgery. Both of these two cases were in high risk group and they did not receive adjuvant treatment because imatinib was not authorized in Turkey at that time. No lung, brain or bone metastasis were determined.

Histologically most common type was spindle cell (48.4%), following it were epithelioid (15.2%) and mixed (36.4%) types. Of the patients 91.4% was CD117, 82.9% was CD34, 34.3% was SMA, 8.6% was desmin, 34.3% was S-100 positive. PDGFRa mutation was not evaluated in our patients (Table 1).

Of the patients 22 had R0, 7 had R1, and one had R2 resection. 10 patients in high risk group after R0 resection 400 mg/day were received adjuvant imatinib. Other four patients in high group did not receive adjuvant imatinib because drug was not authorized in Turkey at time of diagnosis and one patient did not receive treatment with own choice. In all patients undergone R1 and R2 resection imatinib 400 mg/day was started, and all of these patients are continuing their imatinib treatment without progression. Only in one of the patients receiving adjuvant imatinib recurrence occurred in 2nd year of diagnosis. Three patients were received neo-adjuvant imatinib 400 mg/day for about a year. One patient who received neo-adjuvant imatinib did not accept adjuvant treatment after surgery, and is alive disease free at 44th month of diagnosis. Other two patients did not accept surgery after neo-adjuvant treatment. One of these patients had progression after ten years of stable disease with imatinib treatment, sunitinib was initiated in second line treatment, and is receiving sunitinib for about 9 months. Second patient had clinical and radiological response with neo-adjuvant imatinib but did not accept surgery and left imatinib treatment. After 1,5 years of follow-up period progression was determined and again imatinib was initiated. Treatment of this patient is continuing. Metastasectomy with primary tumor resection was performed in two patients who had peritoneal metastasis at diagnosis. One case with diffuse liver metastasis at diagnosis had liver transplantation after primary tumor control with five years of imatinib treatment. After operation the patient is still on imatinib treatment. No serious adverse events were observed. The most common adverse events were seen as grade 1 and fatigue (36.8%), nausea (24.1%), and edema (24.1%) were the most common. Sunitinib was initiated in second line treatment after imatinib in four patients who had metastasis at diagnosis and who developed metastasis in follow-up period. Regorafenib was initiated in two of these patients in third line setting after progression, but could not be continued because of adverse events.

Median follow-up time of the patients was 34

Table 1 Patient characteristics

	No of patients n=35	
	n	**%**
Gender (n)		
Male	17	48.6
Female	18	51.4
Tumor site (n)		
Stomach	17	48.6
Small intestine	11	31.4
Large intestine	1	2.9
Other	6	17.1
Tumor size (cm)		
<2 cm	1	2.9
2.1–5 cm	7	20
>5 cm–≤10 cm	16	45.7
>10	11	31.4
Mitoses/50 HPF		
<5	16	48.5
≥5 to ≤10	5	15.2
>10	12	36.4
Risk categories (n)		
Very low risk	0	0
Low risk	3	8.6
İntermediate risk	11	31.4
High risk	21	60
Histology (n)		
Spindle	16	48.4
Epithelioid	5	15.2
Mixed	12	36.4
CD117		
Positive	32	91.4
Negative	3	8.6

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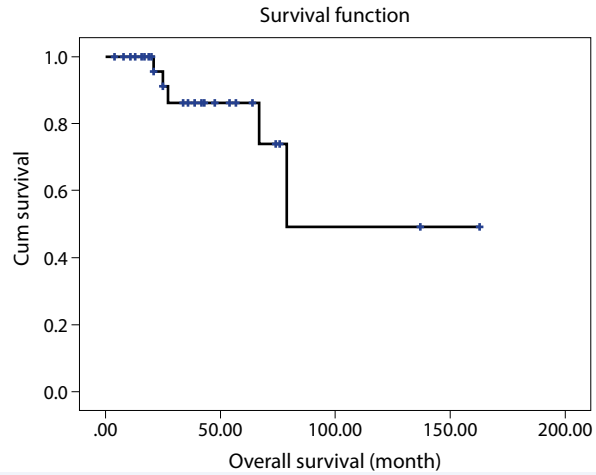

Fig. 1. Median overall survival.

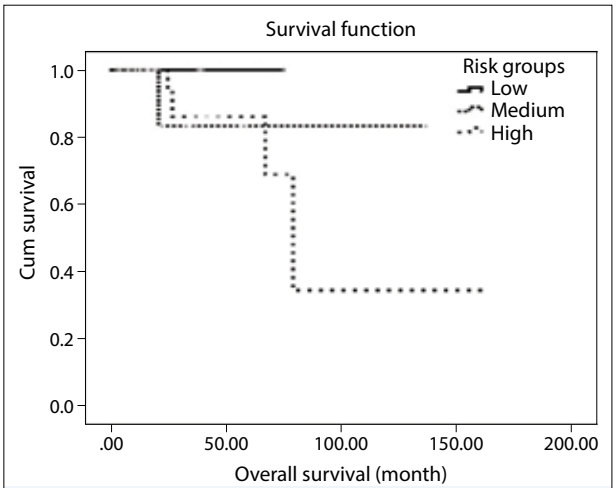

Fig. 2. Survival in relation to risk stratification.

months (4–163), and median OS was 79 months (Figure 1). 1, 3, and 5 year OS rates were 97%, 91.4%, and 91.4%; respectively. Recurrence free survival (RFS) was 67 months for patients who had R0 resection. First line treatment responses in recurrent or metastatic disease were 66.7% stable disease, 25% partial response, and 8.3% progressive disease. Median progression free survival (PFS) was 45±14.2 (95%Cl 17.1–72.9) months with first line treatment in metastatic disease. No difference was determined in survival analysis in terms of gender, tumor size, mitosis rate, tumor localization, and surgery type (Figure 2). Metastasis was not determined in any of the patients who had <5 mitoses/50 HPF, but in 5 of 12 patients who had >10 mitoses/50 HPF metastasis was determined (p=0.015) (Table 2). One patient was not included in this analysis because of

Table 2 Relationship between metastasis and mitosis

	Mitosis			p
	≤5/50	6–10/50	>10/50	
Metastasis				
Yes	0	2	5	0.015
No	16	3	7	

the lost in follow-up period. Five patients were passed away. Four of these patients had liver metastasis, and all of them had progression under treatment.

Discussion

GIST is the most common mesenchymal tumor of GIS. It was classified in soft tissue sarcomas in the past. Since year 1999, GIST terminology has been used owing to usage of morphological, immunohistochemical, and molecular technics.[3] Actual treatment option for primary resectable disease is radical surgery with negative surgical margins. But recurrence risk is high.[10] Marked improvement was achieved in treatment outcomes and OS in recent years with the understanding of molecular mechanism of the disease and development of systemic tyrosine kinase inhibitors.[10] Median age of the patients in our study was 54, and concordant with literature findings. While male dominance has been observed in many case series,[15,16] in some studies it was dispersed equally concordant with our study.[17] The most common localizations were stomach (48.6%) and small intestines (31.4%). Localization in non-GIS regions was 17.1%, and was concordant with many studies in literature.[11,15] The most common complaints at admission were nonspecific complaints such as abdominal pain, bleeding and abdominal mass. These results were discordant with some results reported in literature.[8]

57.1% of the patients were diagnosed with surgery, and 37.1% with endoscopic biopsy in our study. High rate of patients diagnosed with surgery might be associated with high number of operable patients. If the patient has a resectable disease, biopsy may not be performed because of bleeding and intraperitoneal seeding.[15]

About 15–50% of GIST is metastatic at diagnosis. The most common metastasis localizations are liver and peritoneum. Metastasis to regional lymph nodes and extra abdominal sites is very rare, although bone and lung metastasis are reported in literature they are also very rare.[11] In our study 6/35 (17.1%) of the patients were metastatic at diagnosis and concordant with literature findings. Also in our patients the most

common metastasis localizations were liver (four cases) and peritoneum (two cases).

Biopsy material and immunohistochemical evaluation is necessary for exact diagnosis. In a study of Wong et al. it was reported that C-kit (CD117) was positive in 95%, CD34 in 70%, and smooth muscle actin in 30–40% of GIST cases.[18] In our case series CD117 was positive in 91%, CD34 in 82%, and smooth muscle actin in 34% of the patients and our findings is concordant with literature.

73% of the patients that undergone surgery had R0 resection. Our ratios were higher than the ratio (47%) reported in series of DeMatteo et al.[8] The localization of primary tumor in R0 resected patients were mainly stomach and small intestines. Recurrence or progression rates of R0 resected patients were lower than metastatic patients (67 months vs 45 months).

Actual risk group was classified according to Joensuu risk criteria[14] that includes tumor diameter, mitotic ratio, tumor localization, and presence of rupture. In this study most of the patients were in high risk group (60%). Although this ratio was concordant with the data of an earlier multicenter study performed in our country,[15] it was higher than reported in literature.[19] Tumor diameter, mitosis rate, tumor localization, and surgical procedure were determined as prognostic factors in many studies.[19,20] No difference was determined between these parameters and median OS in our study. Our findings were not concordant with these studies. The possible reason of this may be the low number of patients and retrospective design of our study. But mitosis rate in 50 HPF was significantly higher in metastatic patient group (p=0.015).

Dematteo et al. in their landmark randomized controlled trial had shown that 1 year adjuvant imatinib improves RFS.[21]. Later in the phase 3 randomized trial performed by Joensuu et al. RFS was longer in the 36-month group compared with the 12-month group (5-year RFS, 65.6% vs 47.9%, respectively).[9] Adjuvant treatment period of three years had become standard after this trial. Standard adjuvant treatment period was also planned as three years in our study. Recurrence after two years was determined in only one patient that received adjuvant treatment. Efficacy of imatinib in metastatic and unresectable GIST has been reported in many studies [22].

Conclusion

Consequently, the most important treatment option for GIST is radical surgery. Because GISTs very rarely metastasize to lymph nodes unlike adenocarcinomas, generally lymphadenectomy is not necessary. In cases that cannot be totally excised surgically, recurrent, metastatic or the general status of the patient is not suitable for surgery and in cases that need high risk surgery, imatinib is the first preferred treatment option. Patient should be re-evaluated for surgery after tumor regression with medical treatment. Adjuvant imatinib should be initiated in patients with high risk after operation. Although the evident limitations of this study are its retrospective design and low number of patients, it is expressive in terms of our regional data. This study supports that imatinib which is a very tolerable drug with minimal adverse effects in many patients decreases recurrence rate and improves recurrence free survival in adjuvant treatment.

Disclosure Statement

The authors declare no conflicts of interest.

References

1. Kindblom LG, Remotti HE, Aldenborg F, Meis-Kindblom JM. Gastrointestinal pacemaker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. Am J Pathol 1998;152(5):1259–69.
2. Miettinen M, Majidi M, Lasota J. Pathology and diagnostic criteria of gastrointestinal stromal tumors (GISTs): a review. Eur J Cancer 2002;38:39–51.
3. Miettinen M, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. Arch Pathol Lab Med 2006;130(10):1466–78.
4. Hirota S, Isozaki K, Moriyama Y, Hashimoto K, Nishida T, Ishiguro S, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science 1998;279(5350):577–80.
5. Heinrich MC, Corless CL, Demetri GD, Blanke CD, von Mehren M, Joensuu H, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol 2003;21(23):4342–9.
6. de Silva CM, Reid R. Gastrointestinal stromal tumors (GIST): C-kit mutations, CD117 expression, differential diagnosis and targeted cancer therapy with Imatinib. Pathol Oncol Res 2003;9(1):13–9.
7. Roberts PJ, Eisenberg B. Clinical presentation of gastrointestinal stromal tumors and treatment of operable disease. Eur J Cancer 2002;38 Suppl 5:37–8.
8. DeMatteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff

Turk J Oncol 2017;32(1):19-24
doi: 10.5505/tjo.2017.1523

JM, Brennan MF. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. Ann Surg 2000;231(1):51–8.
9. Joensuu H, Eriksson M, Sundby Hall K, Hartmann JT, Pink D, Schütte J, et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. JAMA 2012;307(12):1265–72.
10. Dematteo RP, Heinrich MC, El-Rifai WM, Demetri G. Clinical management of gastrointestinal stromal tumors: before and after STI-571. Hum Pathol 2002;33(5):466–77.
11. Fletcher CD, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, et al. Diagnosis of gastrointestinal stromal tumors: A consensus approach. Hum Pathol 2002;33(5):459–65.
12. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol 2006;23(2):70–83.
13. Rutkowski P, Bylina E, Wozniak A, Nowecki ZI, Osuch C, Matlok M, et al. Validation of the Joensuu risk criteria for primary resectable gastrointestinal stromal tumour - the impact of tumour rupture on patient outcomes. Eur J Surg Oncol 2011;37(10):890–6.
14. Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumor. Hum Pathol 2008;39(10):1411–9.
15. Seker M, Sevinc A, Yildiz R, Cihan S, Kaplan MA, Gokdurnali A, et al. Prognostic factors in gastrointestinal stromal tumors: multicenter experience of 333 cases from Turkey. Hepatogastroenterology 2013;60(124):768–75.
16. Bhalgami R, Manish K, Patil P, Mehta S, Mohandas KM. Clinicopathological study of 113 gastrointestinal stromal tumors. Indian J Gastroenterol 2013;32(1):22–7.
17. Sturgeon C, Cheifec G, Espat NJ. Gastrointestinal stromal tumors: a spectrum of disease. Surg Oncol 2003;12:21–6.
18. Wong NA, Young R, Malcomson RD, Nayar AG, Jamieson LA, Save VE, et al. Prognostic indicators for gastrointestinal stromal tumours: a clinicopathological and immunohistochemical study of 108 resected cases of the stomach. Histopathology 2003;43(2):118–26.
19. Cao H, Zhang Y, Wang M, Shen DP, Sheng ZY, Ni XZ, et al. Prognostic analysis of patients with gastrointestinal stromal tumors: a single unit experience with surgical treatment of primary disease. Chin Med J(Engl) 2010;123(2):131–6.
20. Fujimoto Y, Nakanishi Y, Yoshimura K, Shimoda T. Clinicopathologic study of primary malignant gastrointestinal stromal tumor of the stomach, with special reference to prognostic factors: analysis of results in 140 surgically resected patients. Gastric Cancer 2003;6(1):39–48.
21. Dematteo RP, Ballman KV, Antonescu CR, Maki RG, Pisters PW, Demetri GD, et al. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. Lancet 2009;373(9669):1097–104.
22. Verweij J, Casali PG, Zalcberg J, LeCesne A, Reichardt P, Blay JY, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. Lancet 2004;364(9440):1127–34.