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Original Article

Gastrointestinal stromal tumors: Factors affecting prognosis and single-center surgery results

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Abstract

Aim: Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. The aim of this study was to investigate the clinical features and histopathological findings of GIST cases who underwent surgical treatment in our clinic in terms of prognostic criteria.

Material and Methods: The patients operated for GIST between January 1, 2007 and May 31, 2014 were included in this study. Demographic data, presenting symptoms, ASA scores, diagnostic methods, tumor localizations, use of imatinib before surgery, surgical treatment methods, postoperative complications, tumor size, mitotic activity, immunohistochemical markers, prognostic risk classification, follow-up periods, use of imatinib after surgery, recurrence status and survival data were examined

Results: A total of 60 patients were included in the study. The median age was 56.5 (29-81) years . Fifty five of patients were males. Synchronous tumors in more than one location existed in approximately 7% of the patients. The surgical margin was positive in 14 (23.3%) patients after the surgical procedure. The recurrence and metastasis rates of these patients were 14.3% and 42.8%, respectively. On the other hand, these rates were 10.8% and 17.3% respectively in the patients with negative surgical margin. The expected 5-year survival rates according to the risk classification was 66.7% for very low-risk patients, 85.7% for low-risk patients, 59.7% for moderate-risk patients and 47.7% for high-risk patients.

Conclusion: GISTs have relatively good prognosis compared to epithelial malignant tumors but require long-term follow-up. In addition, satisfactory results can be obtained with the use of tyrosine kinase inhibitors and adequate surgical margins.

Keywords: Mesenchymal Tumor; Tyrosine Kinase; Wedge Resection; Colorectal; Imatinib.

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are located primarily in the gastrointestinal tract and rarely seen. However, GIST is the most common mesenchymal tumor of the digestive tract and it constitutes 80% of the mesenchymal tumors of the gastrointestinal tract (GI tract) (1). These tumors, most commonly seen at the age of 50-60 years, may be located in every region of the gastrointestinal tract. It is mostly seen in the stomach (50-60%) and small intestine (20-30%). In addition, GISTs were also detected in non-gastrointestinal locations such as omentum, peritoneum, retroperitoneum and gallbladder (2). To date, several prognostic factors including localization, tumor size, necrosis, mitotic activity, nuclear atypia, mucosal invasion, and cellularity were proposed to determine GIST prognosis. However, the most important morphological criteria used to determine GIST prognosis are tumor diameter and mitotic index.

For localized primary GIST, curative surgical resection is still a mainstay of therapy. However, after curative surgery, the rate of tumor relapse is still high, especially in high-risk patients (3). The clinical behavior of GISTs is difficult to predict. Therefore, very low risk, low risk, moderate risk and high risk definitions are started to be used instead of malignant - benign tumor terminology (4). In recent years; "recurrence risk scoring" systems showing in which patient group the targeted therapy agents will be useful for the treatment of GIST, are investigated. Ki-67 is determinant in predicting malignant potential of GISTs and it is accepted that the index is a significantly worse prognostic criteria when it is over 10% (5). We aimed to investigate the clinical features, histopathological

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findings and prognostic characteristics of the individuals who were treated by our clinic because of this disease whose the prognosis and clinical behavior indicators are not completely determined.

MATERIAL and METHODS

The patients underwent surgery for gastrointestinal stromal tumor in General Surgery Department of Lutfi Kirdar Kartal Training and Research Hospital between January 1, 2007 and May 31, 2014 were included in this study with the Ethical Committee approval (89513307/1009/328). Patient data were compiled with retrospective file scanning method. Demographic data, presenting symptoms, ASA scores, diagnostic methods, tumor localizations, use of imatinib before surgery, surgical treatment methods, postoperative complications, tumor size, mitotic activity, immunohistochemical markers, prognostic risk classification, follow-up periods, use of imatinib after surgery, recurrence status and survival data were examined. In our study, mitotic activity was determined according to the number of mitosis per 50 high magnification fields. In our study; the index (5), which was accepted in the American National Institutes of Health (NIH) Consensus Conference and was published by Fletcher et al. in 2002, was used as prognostic index. In this index, GISTs were grouped into risk groups in terms of the probability of recurrence or metastasis according to size and mitotic rate. Patients whose follow-up data could not be reached were excluded. Besides, patients who had the another primary cancer in addition to GIST were not included in survival analysis. Statistical analysis of the data was performed using Statistical Package for the Social Sciences (SPSS) for Windows version 20.0 (IBM Corp, Armonk, NY) in computer environment. The average of quantitative data was shown as median (minimum-maximum) or mean ± standard deviation. Qualitative data were expressed as number (n) and percentage (%). In our study, quantitative data were compared with Student's T and One Way Anova tests, and qualitative data were compared with Chi-square test. Survival analyzes were performed with Kaplan-Meier method. $P < 0.05$ value was considered statistically significant.

RESULTS

A total of 60 patients were included in the study. Twenty-seven (45%) of the patients were females and 33 (55%) were males. The median age was 56.5 (29-81). When the presenting symptoms of the patients were evaluated; it was detected that 8 (30%) of the patients had abdominal pain, 12 (20%) had GI bleeding, 9 (15%) had nausea and vomiting, 7 (11.7%) had palpable mass, 4 (6.6%) had anemia, 2 (3.3%) had perforation symptoms and 1 (1.7%) had acute mechanical intestinal obstruction (AMIO) symptoms. The lesions were detected incidentally in 7 patients (11.7%). Clinical diagnostic methods in our study were computed tomography in 28 (46.7%) patients, upper gastrointestinal (UGI) endoscopy in 16 (26.7%) patients, peroperative findings in 9 (15%) patients, ultrasonography in 4 (6.7%) patients, and colonoscopy in 3 (5%) patients. The mean American Society of Anesthesiologists (ASA) Score was often III (48%). Tumors were located in the stomach of 28 patients (%46.7) [in greater curvature of stomach in 18 patients (30%), in lesser curvature of stomach in 7 patients (% 11.7), in stomach antrum in 3 patients (5%)], in the small intestine of 19 patients (31.7%), in the colon of 4 patients (6.7%), in the duodenum of 3 patients (5%) and in the rectum of 2 patients (3.3%). In 4 patients, synchronous tumor was detected in more than one location (6.7%) [small intestine and colon involvement in 2 tumors (%3.3), duodenum and colon involvement in 1 tumor (%1.7) and stomach and small intestine involvement in 1 tumor (%1.7). Extra-gastrointestinal synchronous tumors were detected in 7 patients (Table 1).

Table 1. Locatizations of Synchronous Tumors

Localization	Histology	Number
	Signet-ring cell carcinoma	3
Stomach	Adenocarcinoma	1
	Neuroendocrine tumor	1
Colon	Adenocarcinoma	1
Pancreas	Neuroendocrine tumor	1

Segmental small bowel resection was performed in 16 patients (26.7%), gastric wedge resection in 14 patients (23.3%), subtotal gastrectomy in 8 patients (13.3%), total gastrectomy in 5 patients (8.3%), segmental colon resection in 4 patients (6.7%), Whipple procedure in 3 patients (5%), mass excision in 3 patients (5%), segmentary colon resection in addition to segmentary small bowel resection in 2 patients (3.3%), low anterior resection in 2 patients (3.3%) and segmental colon resection in addition to segmental duodenum resection in 1 patient (1.7%). Incisional biopsy was performed in 2 patients who were considered as preoperative unresectable. The median hospital stay was 7 days (1-39).

In the histopathological examinations of resectable tumors, the median number of tumors was 1 (1-10) and the median tumor size was 6.5 cm (0.1-35). The median size of the tumors located in the stomach was 6.7 cm (0.1-15), the median size of the small intestine tumors was 6.5 cm (0.4-15), the median size of the tumors located in the colon-rectum was 7 cm (3-35) and the mean size of the tumors located in the duodenum was 14.7 ± 4.7 cm. The surgical margin was positive in 14 patients. It was detected that 2 of these patients (14.3%) had recurrence and 6 (42.8%) had metastasis. The median distance of closest surgical margin was 13.5 cm (1-95) in patients with negative surgical margins. The median number of mitosis in tumor specimens was 3.5 /50 HMF (0-71). The median Ki67 score was 3.5 (0-80) . The patients were categorized according to the Fletcher Risk Classification (Figure 1).

Postoperative surgical complications developed in 8 patients (13.3%) (Table 2).

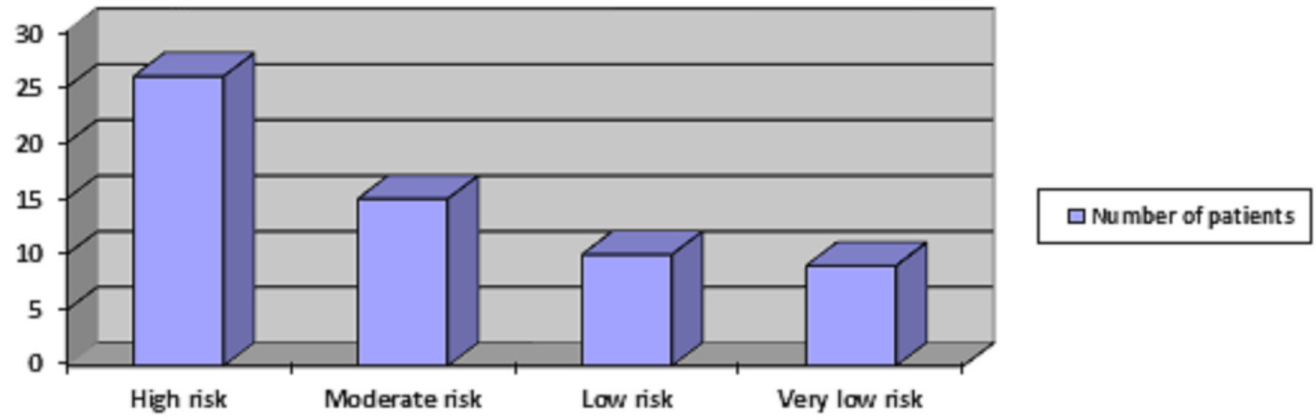

Figure1. Number of Patients according to Fletcher Scoring

Table 2. Characteristics of Patients with Complication

Complication	Localization	ASA	Treatment	Reoperation	Result
	Rectum	1	Low anterior resection	Control bleeding	Exitus on the post-op 27th dmonth
Bleeding (n: 3)	Small intestine	2	Segmental small bowel resection	No reoperation	Discharge on the post-op 10th dmonth Alive
	Stomach + Small intestine	3	Mass excision	Control bleeding	Exitus in ICU on the post-op 1st dmonth
	Duodenum	1	Whipple procedure	No reoperation	Discharge on the post-op 15th dmonth Alive
Bile fistula (n: 2)	Duodenum	3	Whipple procedure	No reoperation	Discharge on the post-op 12th dmonth Exitus on the post-op 28th month
Anastomosis leak (n: 1)	Small intestine	3	Segmental small bowel resection	Reoperation on the post-op 3rd dmonth (double-barreled ileostomy)	Exitus on the post-op 28th dmonth
Wound infection (n: 2)	Stomach	3	Subtotal gastrectomy	No reoperation	Discharge on the post-op 10th dmonth Exitus on the post-op 55th month
	Stomach	3	Wedge resection	No reoperation	Discharge on the post-op 7th dmonth Alive

Preoperative imatinib treatment was given to two patients who were accepted as inoperable with imaging methods. Imatinib treatment was continued for 12 months in one of theses patients and 36 months in another. Tumor resection was performed in these two patients. Imatinib was administered to 24 patients postoperatively (mean duration of imatinib use was 22 months (2-38).

The median follow-up period was 30 (0-86) months. In the follow-up period, it was detected that 7 patients (11.6%) had recurrence. The median follow-up period of patients with recurrence was 28 (13-85) months. Only one of these patients was reoperated. Imatinib treatment was administered to the other patients.The recurrence 3 years after second operation was developed in the patient who underwent surgical resection (Table 3). Metastasis was developed in 16 patients during the follow-up period. The metastasis was found in the liver of 10 patients, in the abdomen of 3 patients, in the ovary of 1 patient, in the mediastinum of 1 patient, in the liver and bone of 1 patient. There was synchronous gastric tumor in 2 of the patients with liver metastases. The primary tumor of the metastasis could not be determined (Table 4). Metastasis ($p=0.01$) increased at statistically significant level as the risk level of the patients increased. Nevertheless recurrence rates is not significant but suggestive ($p=0.05$) (Table 5-6). The expected survival time was 58.5 months for all patients (Table 7).

Table 3. Characteristics of Patients with Recurrence

Localization	ASA	Operation	Tumor size	Risk score	Surgical margin	Imatinib
Small bowel	2	Segmental small bowel resection (Reoperation +)	10 cm	High	Positive	28 months
Small bowel	2	Segmental small bowel resection	15 cm	High	Positive	30 months
Lesser curvature of the stomach	3	Total gastrectomy	22 cm	High	12 cm	36 months
Greater curvature of the stomach	4	Subtotal gastrectomy	2 cm	Very low	20 cm	No use
Gastric antrum	4	Subtotal gastrectomy	6 cm	Very low	40 cm	No use
Duodenum	3	Whipple procedure	9 cm	Moderate	95 cm	No use
Colon	2	Segmental colon resection	23 cm	High	Positive	36 months

Table 4. Characteristics of Patients with Metastasis

		Number of patients (n)	Percent (%)
Tumor size	<2	0	0
	2-5	3	21.4
	5-10	2	14.3
	>10	7	50
	Biopsy (Tumor size was not evaluated)	2	14.3
CD 117 (+)		13	92.8
CD 34 (+)		13	92.8
S100 (+)		3	21.4
Mitotic index	<5	3	21.4
	5-10	2	14.3
	>10	9	64.3
Imatinib treatment		12	85.7
Localization	Stomach	4	28.5
	Small bowel	4	28.5
	Colon	3	21.4
	Duodenum	1	7.2
	Rectum	1	7.2
	Small bowel + colon	1	7.2
Risk score	Very low	2	14.3
	Low	0	0
	Moderate	1	7.2
	High	11	78.5
Surgical margin	Pozitif	8	57.2
	Negatif	6	42.8

Table 5. Distribution of Metastasis Development According to Risk Score

		Metastasis		Total	P
		Absent	Present		
Risk score	Very Low	2	1	3	0.017
	Low	9	0	9	
	Moderate	13	1	14	
	High	14	11	25	
Total		38	13	51	

Table 6. Evaluation of Recurrence Development According to Risk Score

		Recurrence		Total	P
		Absent	Present		
Risk Skoru	Very Low	2	1	2	0.05
	Low	9	0	9	
	Moderate	14	0	14	
	High	20	5	20	
Total		45	6	45	

Table 7. Expected Survival

Expected Survival			
Expected	Std. Error	95% Confidence interval	
		Lower Limit	Upper Limit
58.536	5.232	48.281	68.792

The expected 5-year survival rate was 53.1% (Figure 2). In our study; the expected 5-year survival rates of the patients according to the risk classification was 66.7% for very low-risk patients, 85.7% for low-risk patients, 59.7% for moderate-risk patients and 47.7% for high-risk patients (Figure 3). While the expected 5-year survival rate was 32.9% in patients with distant metastases, 68.1% was in patients without metastasis (Figure 4). While the expected 5-year survival rate was 33.3% in patients with recurrence, 60.7% was in patients without recurrence (Figure 5). The

expected 5-year survival rate in patients with positive and negative surgical border was same (53.1%) (Figure 6) While the expected 5-year survival rate in patients using imatinib was 54.4%, it was 53.8% in untreated patients (Figure 7).

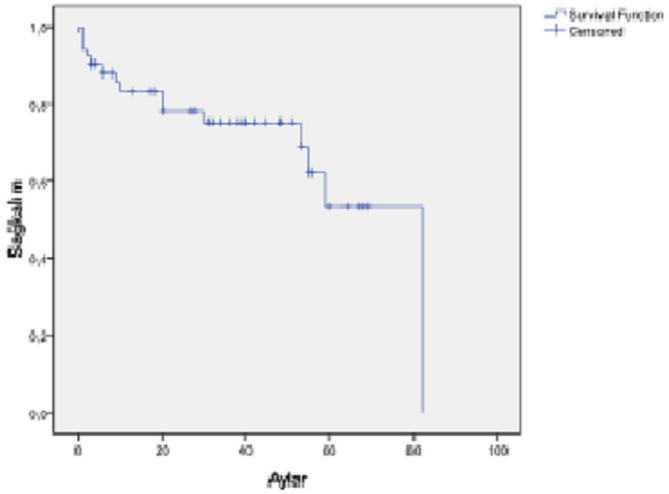

Figure 2. Annual Expected Survival

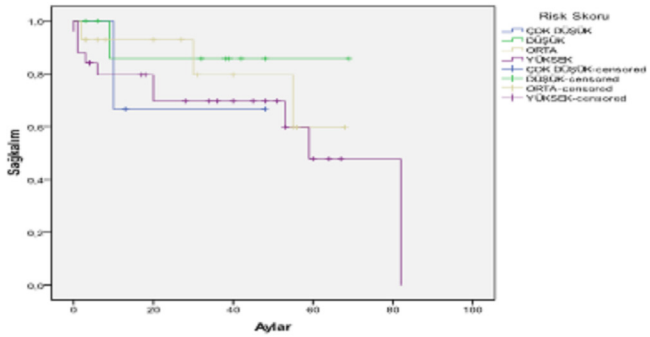

Figure 3. Survival by Risk Classification

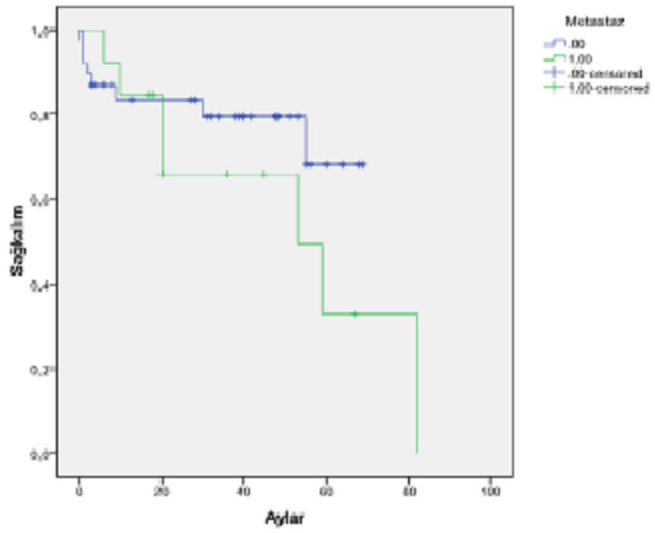

Figure 4. Survival in Patients with Distant Metastasis

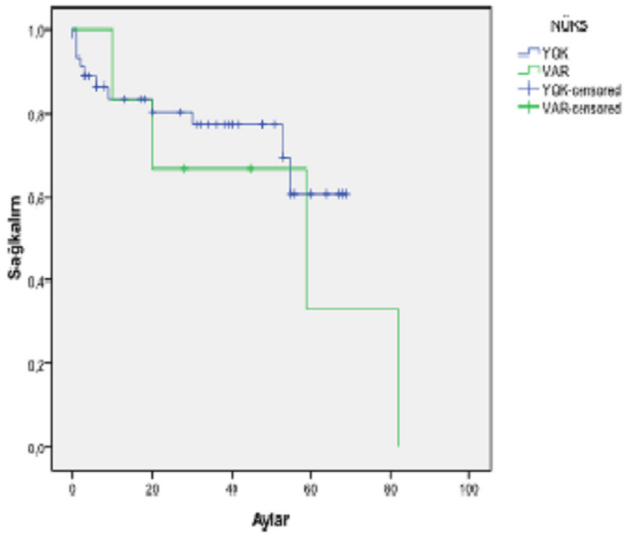

Figure 5. Survival in Patients with Recurrence

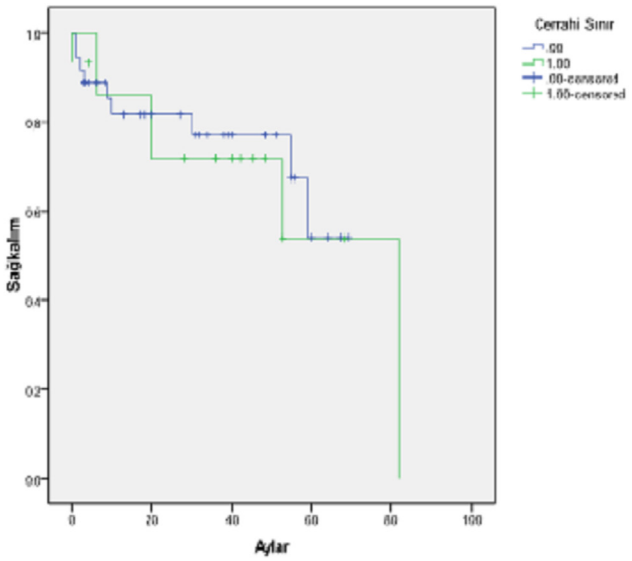

Figure 6. Survival in Patients with Positive Surgical Border

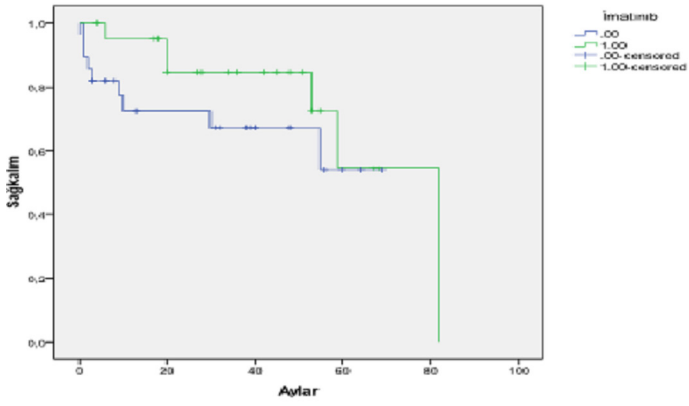

Figure 7. Survival in Patients Using Imatinib

DISCUSSION

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors along the gastrointestinal tract and typically occur in elderly individuals. The median age in the major series is usually reported between 60-65. In our study, the median age was 57 and range was 29-81 years. GISTs under the age of 40 are relatively rare and it was reported that the only 1% of cases were under 21 years of age (7). In our study, only 4 patients (7.5%) were under the age of 40 and all patients were over 30 years of age.

More than half of the GISTs reported in the literature are seen in the stomach, 30% in the jejenum or ileum, 5% in the duodenum, 5% in the rectum and slightly below 1% in the esophagus (7). The origins of GISTs appearing in the parenchymal organs, which are outside of the gastrointestinal tract, such as the pancreas and liver remain controversial. A group of authors claim that they are metastases or the spread of the gastrointestinal tract. Similarly in our study; while the tumors in half of the patients were located in the stomach, this was followed by small intestine, colon and duodenum respectively. Synchronous tumors in more than one location existed in approximately 7% of the patients.

In the literature, the most common clinical symptoms of GISTs are bleeding and ulcer-like pain. The bleedings in these patients may occur in conditions ranging from chronic anemia caused by occult bleeding to life-threatening acute hematemesis. Apart from these, emergency situations such as intestinal obstruction and tumor rupture may occur more rarely. In the literature, the tumors in approximately one third of patients are incidentally detected during imaging or surgical procedures performed for other reasons (7). In our study, the most common symptom was abdominal pain (29%). The rate of patients presenting with acute GI bleeding was 20%, and the rate of patients presenting with chronic anemia was approximately 7%. There was palpable mass in approximately 12% of the patients. The rate of patients diagnosed incidentally was approximately 12%. Compared to the literature, the two prominent points in our findings are the low rate of incidentally diagnosed patients and the high rate of the palpable mass meaning advanced disease. This depends on that the hospital admission process of our patient population was long.

The prognostic parameters of GISTs were tried to be determined as a result of the analysis of large series with long-term follow-up. These parameters include tumor size, mitotic rate, tumor localization, kinase mutation status and tumor rupture. However, there are two universally accepted parameters in all these parameters. These two parameters are tumor size, and mitotic rate at 50 HMF. Nowadays, there are a number of prognostic indices covering the above-mentioned parameters. The most commonly used one of these was the index which was accepted in the American National Institutes of Health (NIH) Consensus Conference (7) and was published by Fletcher et al., in 2002 (6) and we also used this index in our study. In this index, GISTs were grouped into risk groups in terms of the probability of recurrence or metastasis according to size and mitotic rate. Another prognostic staging system of North American origin is The Armed Forces Institute of Pathology (AFIP) system developed by Miettinen et al. In this system, anatomic localization in addition to size and mitotic index was added to prognostic factors because of the possibility of metastasis. According to this system, the prognosis of gastric tumors is accepted to be better (7). Similarly, the Memorial Sloan Kettering Cancer Center (MSKCC) developed a nomogram that revealed the possibility of disease-free survival at the end of a study with 127 patients (8). This nomogram includes the tumor size, mitotic index, tumor localization. NIH system was used for risk assessment in our study and the prognosis of patients with low risk was found to be better than the patients with moderate and high risk according to this system.

Nowadays, wedge resections are the most commonly used methods in the surgery of gastric GISTs. With wedge resections, small and medium sized gastric GISTs can be removed with adequate surgical margins. Total gastrectomy may be necessary for large tumors which have a large area in the stomach, multiple tumors and recurrent tumors. Distal gastrectomy can also be performed in tumors with involvements of the pylori and wide lesser curvature. The preferred method for localized intestinal tumors is segmental resections. There are differences in the results about the microscopic negative surgical margins after resection. In a retrospective study with 819 patients conducted by McCarter et al., it was seen that the R1 resection did not affect prognosis and disease-free survival, after 4 years of follow-up (9). However, in a retrospective series with 151 patients conducted by Catena et al., it was detected that the surgical margin positivity negatively effected the 5-year disease-free survival (10). In our study, surgical margin was positive in 14 (23.3%) of our patients. The recurrence and metastasis rates of these patients were 14.3% and 42.8%, respectively. On the other hand, these rates were 10.8% and 17.3% in the patients with negative surgical margins, respectively. These findings suggest that surgical margin positivity may be a poor prognostic factor in our series.

The majority of GISTs reported in current literature are local tumors smaller than 5 cm. Generally, it was reported that the small intestinal GISTs were detected to be larger and the small intestinal GISTs metastasize at high rate compared to gastric GISTs. The typical sites of GISTs metastases are peritoneal cavity and liver. Although rare, bone metastases are also reported. Unlike other sarcomas, lung metastases of GISTs are almost non-existent. Lung metastases of GISTs with widespread metastases are reported rarely (11-18). Although metastases of GISTs usually occur within one to two years, there are also reported cases of metastasis occuring after many years. In the literature, there is a case-report of liver metastasis that occurred after 42 years. This suggests that patients

should be followed for a long time (7). In our study, the mean tumor size was 8 cm and the lung and peritoneal metastases were detected in the majority of patients with metastasis. The detection of tumors at larger size than the literature is another finding that strengthens the idea of late admission to hospital. In addition, the rate of detection of metastases in our study (34 months) was similar to the literature. Unlike the literature, the possibility of metastasis (66%) and tumor size (16.1 cm) were most commonly seen in colorectal tumors.

Following detection of KIT or PDGFRα mutations in GISTs, these tumors were the first solid tumors that became targets of tyrosine kinase inhibitor treatments. In Z9001 phase-III study conducted by the American College of Surgeons Oncology Groups, the patients with tumors larger than 3 cm were divided into two groups, one group received imatinib and the other group received placebo. At the end of the median value of 19.7 months, it was detected that 1-year recurrence rate was 2% in the imatinib group and 17% in the placebo group. This study showed that adjuvant imatinib treatment reduced the possibility of recurrence in moderate and high risk patients (19,20). In the Phase 2 qualified US Intergroup ACOSOG Z9000 study that included 106 patients and was evaluated by the same team, it was planned that the Imatinib treatment (400 mg/day) was administered to high-risk patients (patients with a tumor greater than 10 cm, patients with tumor rupture, and patients with peritoneal metastasis) for one year. This treatment was completed in 82% of the patients. In this study; at the end of median 4 years follow-up, it was found that one-year recurrence was 6%, two-year recurrence was 27% and three-year recurrence was 39% (21). In our study, recurrence rate was 11.6% during the 32-month follow-up period. The data of our study cannot be fully compared with these comprehensive studies. In our study, the patient group is in a wide range according to the risk levels. In general, however, it can be said that the recurrence rates in our study are similar to rates reported in the literature.

Nowadays, surgery of GISTs metastases is performed in only selected cases as a result of the discovery of imatinib treatment. The surgical indications of GIST metastases are limited to cases with imatinib-resistant and cases with metastasis-related complications (22). In our study, no patients underwent surgical treatment due to metastasis.

CONCLUSION

GISTs have relatively good prognosis compared to epithelial malignant tumors but require long-term follow-up. In addition, satisfactory results can be obtained with the use of tyrosine kinase inhibitors, and adequate surgical margins.

Limitations

The limitations of our study which has been completed in a single referral center were retrospective design and limited number of patients. As, the incidence of GISTs is lower in the population a multicenter or nationwide study might reveal more accurate results in the future.

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