EJMI

DOI: 10.14744/ejmi.2022.16557
EJMI 2022;6(2):210–216

Research Article

Clinicopathologic Features of Operated Gastrointestinal Stromal Tumors, Adjuvant Therapy Outcomes, and Recurrence-Related Factors

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Abstract

Objectives: We aimed to evaluate the clinicopathological features and clinical outcomes of patients with resected Gastrointestinal stromal tumors (GISTs).

Methods: This study was a retrospective, multicenter cohort study. Patients diagnosed with a GIST, 18 years of age and older, operated on R0, between January 2005 and May 2020 were included in the study. Patient with metastatic disease at diagnosis were excluded.

Results: Of 104 patients, the median age was 61 years (35-87) and 58.7% (n=61) were male. The most common location was stomach (n=52.5%). According to The Modified-National Institutes of Health (M-NIH) classifications, 52 (50%) patients were in the high-risk group. The median relapse-free survival (RFS) was 62.1 (95% CI; 52.7-71.5) months. Increased aged at diagnosis (HR=0.952, 95% CI 0.910-0.995, p=0.030), Ki-67<10% (HR=5.007, 95% CI 1.503-16.680, p=0.009), low risk M-NIH category (HR=21,083, 95% CI 2.119-209.769, p=0.009), two-year adjuvant imatinib (HR= 0.255, 95% CI 0.070-0.920, p=0.037) or three-year treatment (HR=0.191 95% CI 0.040-0.919, p=0.039) were independent factors for RFS.

Conclusion: High ki-67 index and high M-NIH score are factors that have a negative effect on relapse. Keeping the adjuvant treatment period longer than one year and advanced age have a positive effect on recurrence.

Keywords: Adjuvant imatinib treatment, relapse-free survival, operated gastrointestinal stromal tumors

Cite This Article: *Ilhan A, Eraslan E, Demir N, Aslan F, Yildiz F. Clinicopathologic Features of Operated Gastrointestinal Stromal Tumors, Adjuvant Therapy Outcomes, and Recurrence-Related Factors. EJMI 2022;6(2):210–216.*

Gastrointestinal stromal tumors (GISTs) are the most common malignant mesenchymal tumors of the gastrointestinal tract (GI).[1] GISTs account for 0.1-3% of all gastrointestinal malignancies.[2] GISTs occur along the GI tract, most commonly in the stomach (60%) and small intestine (30%), and less commonly in the duodenum (5%), rectum (2-3%), and esophagus (1%).[3] Although it can occur at any age, advanced age is a risk factor for GIST, and the mean age of onset is 60 years.[4]

The curative treatment option for GISTs is surgery. The recurrence rate after surgery varies. Because of the differences in the biological behavior of GISTs and the difficulties in pre-

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Submitted Date: August 18, 2021 **Accepted Date:** March 02, 2022 **Available Online Date:** March 18, 2022

dicting malignant potential, several studies have been performed to determine prognosis. Various scoring systems, including tumor size, mitotic index, and localization, were defined at the end of these studies to assess the risk of recurrence and disease prognosis following resection. Among these risk scoring systems, the Armed Forces Institute of Pathology (AFIP) and the Modified-National Institutes of Health (M-NIH) classifications are the most commonly used.[5-7]

Recurrence in a group of patients with GIST after surgery was the basis for studies investigating the effectiveness of adjuvant therapy. Imatinib was shown to significantly enhance recurrence-free survival in a randomized controlled study published in 2009, one of the first to assess the efficacy of adjuvant therapy in resected GISTs.[8] Discussions on the duration of adjuvant imatinib treatment continued in the years that followed. The Scandinavian Sarcoma Group (SSG XVIII/AIO)'s study showed that treatment with imatinib for at least three years resulted in a significant improvement in overall survival in high-risk GIST patients.[9] Current guidelines recommend using imatinib as an adjuvant after resection for 36 months in patients with intermediate and high-risk GIST.[10]

Although adjuvant treatment with imatinib is used as the standard of care, a group of patients still experience disease recurrence. This study aimed to retrospectively investigate the clinicopathologic characteristics, adjuvant treatment outcomes, recurrence, and survival of patients diagnosed with resected GIST and factors that may be associated using real-world data.

Methods

This study was a retrospective, multicenter cohort study study. Patients followed up with a diagnosis of gastrointestinal stromal tumors in three different centers in Turkey between January 2005 and May 2020 were retrospectively evaluated. The Ethics Committee of Health Sciences University Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (2020-11/878, 25.11.2020) approved before the study.

The study included patients aged 18 years and older who underwent R0 surgery and were diagnosed with a gastrointestinal stromal tumor. Patients who were metastatic at the time of diagnosis and not suitable for surgery were excluded from the study.

Patient (gender, age at diagnosis) and tumor characteristics (anatomic location, tumor diameter, Ki-67 proliferation index, mitotic rate, histologic subtype, immunohistochemical cd 117, and dog-1 positivity), treatment characteristics (adjuvant imatinib treatment and duration), and survival status were recorded by reviewing manual patient files and/or the electronic record system. Patients were staged in accordance with the 8th edition of the American Joint Committee on Cancer (AJCC). Risk groups were determined according to M-NIH criteria.

The primary endpoint of the study was relapse-free survival (RFS). The secondary endpoint was factors that may be associated with RFS and overall survival (OS).

For data analysis, IBM Statistical Package for Social Sciences (SPSS®) v.23 was used. The time from operation to relapse was defined as RFS, and the time from diagnosis to the last control date or death was defined as OS. The Kaplan-Meier method was used for survival analyses, and the log-rank test was used to compare subgroups. Factors that might be associated with RFS were evaluated using Cox regression analysis. A value of $p<0.05$ was considered statistically significant.

Results

The median age of the 104 patients included in the study was 61 years (35-87 years), while 58.7% (n=61) were male. The most common primary location was the stomach 50% (n=52), and the second most common location was jejunum/ileum 32.7% (n=34). According to M-NIH criteria, 50% (n=52) patients were in the high-risk group. Table 1 shows all patient characteristics.

Imatinib was given to 36 % (n=18) of the 48.1% (n=50) patients who got adjuvant therapy for one year, 26 % (n=13) for two years, and 34 % (n=17) for three years. During the median 35.9 (95% CI; 14.3-70.3) months follow-up period, recurrence occurred in 36 (34.6 %6) patients. The median RFS in the entire patient group was 62.1 (95% CI; 52.7-71.5) months. Adjuvant imatinib was not given to 44.5 % (n=16) of the patients, but it was given to 55.5 % (n=20) of the relapsed patients. Table 2 displays treatment-related characteristics.

When patients were grouped by the duration of adjuvant imatinib treatment, the median RFS was 20 months (95% CI; 14.0-26.0) in those receiving 1-year adjuvant imatinib treatment, whereas the median RFS was not reached in those receiving two years. The median RFS for patients who received adjuvant imatinib for three years was 62.1 months (95% CI 50.8-73.4). The 5-year rate of RFS in patients, who had 1-year adjuvant imatinib, was 12.8 %. The 5-year rate RFS for those, who received 2-year and 3-year adjuvant imatinib therapy, was 60.6% and 58.2%, respectively. It was observed that patients treated with imatinib for both two years and three years had a better RFS compared to those treated with imatinib for only one year (p=0.043, p=0.001, Fig. 1).

Examination of RFS by risk group showed that the median RFS was not achieved in patients in the low-risk group. The median RFS was 40.5 months (95% CI; 16.3-64.7) in the intermediate-risk group, and the median RFS was 56.3

Table 1. Main patient and tumors characteristics of study population (n=104)

Characteristics	n	%
Gender		
Female	43	41.3
Male	61	58.7
Age-median-range	61	35-87
Stage		
Stage 1-small intestinal GIST	7	6.7
Stage 1a	19	18.3
Stage 1b	16	15.4
Stage 2	15	14.4
Stage 3a	23	22.1
Stage 3b	24	23.1
Tumor size (cm)		
<2	6	5.8
2-5	36	34.6
5-10	30	28.8
>10	30	28.8
Unknown	2	1.9
Localization		
Gastric	52	50
Doudenum	6	5.8
Jejenum/ileum	34	32.7
Rectum	4	3.4
Extragastrointesinal	8	7.7
Ki-67		
<10%	65	62.5
>10%	28	26.9
Unknown	11	10.6
Mitotic index		
<5/50	53	51
>5/50	48	46.2
Unknown	3	2.9
Histologic subtype		
Spindle cell type	94	90.4
Epitheloid type	3	2.9
Mixed	5	4.8
Unknown	2	1.9
M-NIH risk category		
Low	35	33.7
Medium	17	16.3
High	52	50

M-NIH: Modified-National Institutes of Health ; GIST: Gastrointestinal stromal tumors

(95% CI; 40.9-71.7) months in the high-risk group. The RFS of low-risk patients was significantly better compared to intermediate-risk patients (p<0.001) and high-risk patients (p=0.001). The median RFS rates for intermediate and high-risk groups were similar (p=0.159, Fig. 2). According to the M-NIH risk groups, the 1-year and 3-year RFS rates were

Table 2. Adjuvant treatment features

Characteristics	n	%
Adjuvant imatinib		
Yes	50	48.1
No	54	51.9
Adjuvant duration		
1 year	18	36
2 year	13	26
3 year	17	34
Continue	2	4
Recurrence		
Yes	36	34.6
No	38	65.4
Recurrence surgery		
Yes	9	25
No	27	75

100%, 100%; 93%, 63%; 85%, and 69% in the low-risk, intermediate-risk, and high-risk groups, respectively.

When factors that might be associated with RFS were examined, it was observed that increased age at diagnosis (HR =0.952, %95 CI 0.910-0.995, p=0.030), Ki-67 rate below 10% (HR =5.007, %95 CI 1.503-16.680, p=0.009), low risk of M-NIH category (HR =21.083, %95 CI 2.119-209.769, p=0.009), adjuvant imatinib duration of 2 years (HR =0.255, %95 CI 0.070-0.920, p=0.037) or 3 years (HR =0.191, %95 CI 0.040-0.919, p=0.039) were independent factors for RFS. It is shown in Table 3.

The overall patient group's estimated OS was 152.9 months (95 % CI; 121.2-184.7), with a 10-year OS of 62.5%. The 5-year OS was 89.9% in the low-risk group, 80.7% in the intermediate-risk group, and 76.6% in the high-risk group. There was no significant difference between the risk groups concerning OS (p=0.096, Fig. 3).

There was a significant difference between groups in terms of OS when those who received three years of adjuvant imatinib treatment and those who received one year of imatinib were compared in OS (p=0.001, Fig. 2). There was no statistically significant difference in OS between the 3-year and 2-year adjuvant imatinib groups (p=0.265, Fig. 2).

Discussion

Age at diagnosis, M-NIH risk category, Ki-67, and duration of adjuvant imatinib treatment were identified as independent factors influencing RFS in this study, which evaluated the clinical characteristics and treatment results of GISTs undergoing surgery.

When it comes to the demographics of GISTs, significant cohort studies conducted in various geographies found that

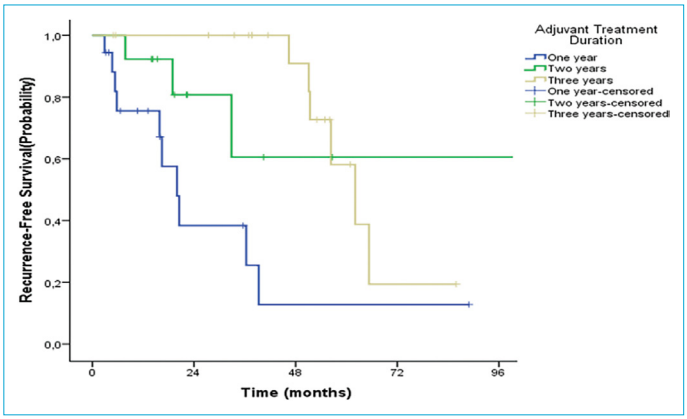

Figure 1. Relapse-Free survival of treated with adjuvant imatinib.

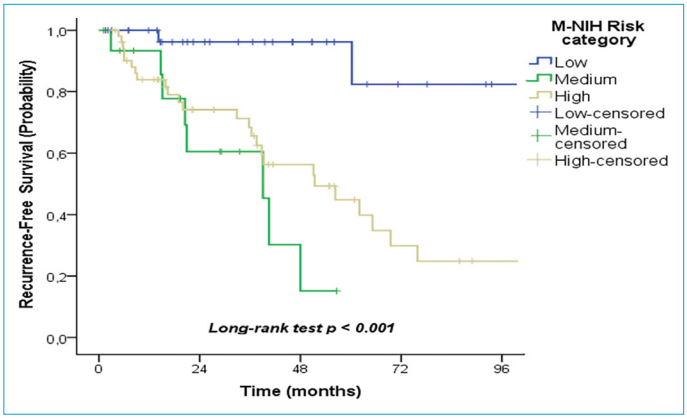

Figure 2. Relapse-Free survival according to M-NIH score (low, medium, high risk groups).

M-NIH: Modified-National Institutes of Health

the median age was around 60, and the gender distribution was nearly equal. While the median age at diagnosis in our patient group is consistent with these data, the number of male patients was higher in our group.[11-13] The information that the most common localization of GISTs is stomach and small intestine is also consistent with our study.[3,11,14] In contrast to previous studies, our GIST cases located in the extra-gastrointestinal tract accounted for approximately 7.7% of our total cohort.[13,15] In addition to ethnic and geographical differences, the fact that we work as a referral center, as mentioned earlier, may explain the higher incidence of extra-gastrointestinal localized cases in our study.

Adjuvant imatinib studies in the treatment of gastrointestinal tumors have formed the basis of recurrence rates of up to 50% following surgical resection. It has been included in the guidelines as a standard treatment since 2009.[8,16] In a multicentre trial in the United States including 107 opereted high risk GIST patients (tm diameter >10 cm or tumor rupture or five peritoneal metastases), the 3-year RFS rate with 1-year adjuvant imatinib was reported 61%.[17] In a similar patient group, the 3-year RFS rate with adjuvant 1-year imatinib was reported as 57% in another multicenter study from Japan.[18] The 3-year RFS rate achieved with 1-year adjuvant imatinib treatment in our study was 38.4%. In the EORTC study, the efficacy of adjuvant 2-year imatinib use was examined, and the 5-year RFS was 69%, whereas this rate was 60.6% in our study.[19] Considering the efficacy of 3-year adjuvant use of imatinib, the 5-year rate RFS in the pivotal SSG XVIII AIO the trial was 71.1%, whereas, in our study, it was 58.2%.[9,20,21] It is thought that ,compared to the mentioned studies, differences in patient characteristics and the small number of patients might be the reason of lower RFS rates with adjuvant therapy in our study.

In a study from China in which RFS rates of 497 GIST patients were evaluated according tothe M-NIH scoring system; respectively low, medium and high risk groups, 1-year RFS rates in ; 100%, 100%, 80%,while the 3-year RFS rate is; ıt was found to be 100%, 93.8%, 53.1%.[12] From our country, Şenol et al.[22] according to the M-NIH scoring system, in low, medium and high risk groups, respectively; 1-year RFS rates: 100%, 90%, 82%, 3-year RFS rates; 100%, 90.2%, 48.9%. RFS rates were found to be higher in the low- and intermediate-risk groups than in the high-risk group in both studies. Although the RFS rates achieved in the low-risk group were better than those in the moderate- and high-risk groups, there was no difference in RFS rates in our study's moderate- and high-risk groups. While all of our high-risk patient group received adjuvant imatinib therapy, half of our patients in the intermediate-risk group were treated with adjuvant therapy. This might be the reason of similar RFS rates obtained in the both intermediate and high-risk groups in our study.

Many studies have attempted to define the factors that determine prognosis in patients with GIST.[23-25] Although tumor size and mitotic activity primarily effect the prognosis, it was thought that factors such as anatomic location and Ki-67 might also be critical prognostic markers.[26-28] In a study of 1022 patients in China, a Ki-67 level of more than 6% was related to a poor prognosis.[29] Another research of 135 patients in Turkey found that having a high Ki-67 level was associated with a poor prognosis.[30] Similarly, Ki-67 >10% was shown to be a negative factor for recurrence in our study.

The M-NIH classification is one of the two most widely used scoring systems for determining the risk of recurrence and disease prognosis following resection.[5-7] In a large series evaluating approximately 500 patients, it was observed that patients with a high-risk score according to the M-NIH scoring system were an independent determinant of OS and RFS compared to the non-high-risk group.[12] According to the M-NIH scoring system, high risk was defined as the most critical factor for recurrence in another study by

Table 3. RFS; Cox Regresssion Analysis

Parameter	HR		95% CI	p
	Lower	Upper		
Gender	1.150	0.394	3.361	0,798
Age	0.952	0.910	0.995	**0.030**
Stage	1.172	0.232	5.925	0.234
Tumor Diameter	0.592	0.135	2.595	0.487
Location of the tumor	0.850	0.356	2.027	0.713
Ki 67	5.007	1.503	16.680	**0.009**
Mitotic index	0.971	0.282	3.336	0.962
M-NIH Risk category	21.083	2.119	209.769	**0.009**
Adjuvant treatment time				
Adjuvant treatment time, 1 year	1.903	0.587	6.172	0.284
Adjuvant treatment time, 2 year	0.255	0.070	0.920	**0.037**
Adjuvant treatment time, 3 year	0.191	0.040	0.919	**0.039**

M-NIH: Modified-National Institutes of Health; RFS: Relapse-free survival; HR: Hazard ratio; CI: Confidence interval

Mucciarini et al.,[1] which included 124 patients diagnosed with GIST. Similarly, in our research, being in the high and moderate M-NIH class was determined to be an independent negative factor for RFS.

In a large series of about 3000 patients in Taiwan, evaluating the factors affecting prognosis in patients with GIST, the patient group was divided into 50, 50-60, 60-70, 80, and younger patients were found to have a better prognosis.[31] Similarly, in a study conducted in our country by Hatipoglu et al.,[30] younger patients reported a better prognosis. Advanced age was also a negative prognostic factor in the Minzhi L study.[31] The conclusion that each unit of age decline in patients with GIST, obtained in our research, negatively affects prognosis needs to be investigated in a more extensive series.

Before the use of adjuvant imatinib, the 5-year overall survival rate in early-stage disease was 40%, but this rate improved to more than 90% with the use of adjuvant imatinib.[8,32] Zhao et al.[33] classified 185 high-risk GIST patients into four groups based on the duration of adjuvant treatment as <1 year, 1-2 years, 2-3 years, and >3 years, and the 5-year OS was reported as 64%, 88%, 88%, and 100%, respectively. Joensuu et al.[9] compared the 1-year adjuvant of imatinib to the 3-year adjuvant of imatinib, and the 5-year rate OS was 92.0% vs. 81.7%. In our study, there was a significant difference in OS between those who received three years of adjuvant imatinib treatment and those who received one year of imatinib treatment, but no statistical difference in OS between those who received three years of adjuvant imatinib treatment and those who received two years of adjuvant imatinib treatment. This result supports the significant contribution of imatinib use longer than one year. The heterogeneity of the patient groups was thought to be why adjuvant imatinib for 2 and 3 years did not make a significant difference in OS.

In the study by Mucciarini et al. evaluating overall survival by risk group in patients with GIST, the 5-year overall survival rate was 90.1%, 93%, and 61.5% in the low-, intermediate-, and high-risk groups, respectively.[1] In the study by Wang et al., sharing their 15-year experience, the 5-year rates OS were 100%, 89.6%, and 65.9% in low-, moderate-, and high-risk groups, respectively.[12] The 5-year overall survival rates by risk group in our study were similar to previous studies.

The limitations of our study were its retrospective nature, the relatively small number of patients, and the shorter median follow-up time compared with this type of well-advanced disease. However, our study is very valuable in revealing the factors influencing recurrence and demonstrating the efficacy of adjuvant therapy.

In conclusion, although GISTs have a good clinical course, a high Ki-67 score, young age, and a high M-NIH score are

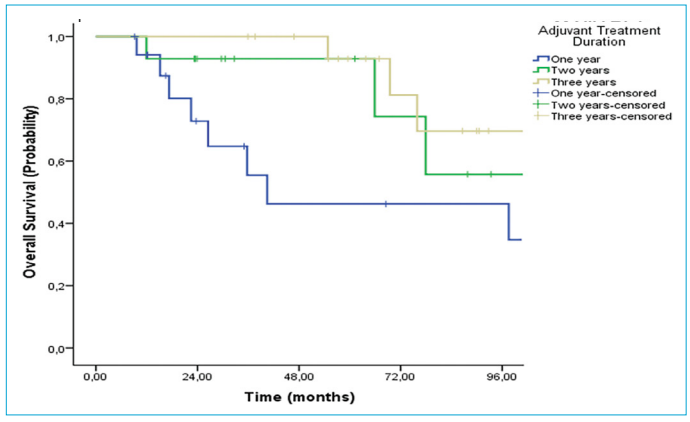

Figure 3. Overall survival of treated with adjuvant imatinib.

factors that negatively affect recurrence. A longer period of adjuvant treatment more than one year has a positive effect on recurrence.

Disclosures

Ethics Committee Approval: The study was approved by The Health Sciences University Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Ethics Committe (Date: 25/11/2020, No: 2020-11/878).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – A.I.; Design – A.I., F.Y.; Supervision – F.Y.; Materials – A.I., N.D., F.A.; Data collection &/or processing – A.I., N.D., F.A.; Analysis and/or interpretation – E.E., F.Y.; Literature search – A.I.; Writing – A.I.; Critical review – F.Y.

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