J Oncol Sci 5 (2019) 73–79

Contents lists available at ScienceDirect

J Oncol Sci

journal homepage: www.journalofoncology.org

Original Article

Effect of clinical and pathological features of gastrointestinal stromal tumors on overall survival and prognosis: Single center experience

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ARTICLE INFO

Article history:
Received 5 July 2019
Accepted 19 October 2019
Available online 31 October 2019

Keywords:
GIST
Overall-survival
Prognosis

ABSTRACT

Aim: Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of the gastrointestinal tract. We aimed to evaluate the clinicopathological features of the patients in Thrace and improve our management.

Material and Method: In this retrospective study, 68 patients with a diagnosis of GIST referred to Trakya University Medical School Hospital between 1997 and 2015 were evaluated.

Results: The most common symptom was abdominal pain (38.2%) and the location was small-intestine (42.6%). Large masses had higher metastasis and relapse rate. The mean tumor size with relapse was 11.8 ± 3.8 cm meanwhile it was 6.5 ± 3.0 cm in non-relapsed patients ($p = 0.01$). The mean size of the tumor was 13.5 ± 4.4 in the metastatic group although this data was 8.8 ± 4.7 cm in the non-metastatic group ($p = 0.01$). With necrotic tumors, mitotic rate and size were higher. The mean mitosis count was 21.0 ± 3.6 in necrotic tumors and 7.2 ± 9.9 in non-necrotic tumors ($p = 0.005$). The mean size was 10.8 ± 5.0 cm in necrotic tumors and 5.6 ± 3.0 cm in non-necrotic tumors ($p = 0.009$). According to AFIP criteria, most of the patients were in the high-risk group (57.4%). Overall survival (OS) was longer in non-smokers and non-drinkers. Median OS was 80.16 months in non-smoker group (95% CI, 27.83–132.49) and 24.64 months (95% CI, 15.49–33.78) in the smoker group ($p = 0.001$). The median OS was 80.09 months in the non-drinker group (95% CI, 13.99–146.20) and 24.64 months (95% CI, 13.18–36.10) in drinker group ($p = 0.05$). Median OS in stomach GIST was 41.39 months, in small-intestine were 80.09 months and in the colon were 35.68 months ($p = 0.032$). Patients underwent surgery had longer overall-survival. Median OS was 80.09 months in patients undergone surgery and 16.98 months in patients had not been operated ($p = 0.001$). Overall survival was longer in GIST with mitotic rate <5/50HPF than with >5/50HPF. Median OS was 80.16 months in patients who had less than 5 mitosis and 39.22 months in higher mitotic rate (95% CI, 31.58–46.87) ($p = 0.034$). Overall survival was shorter in GIST with Ki-67 > 5% than with 5%>. Median OS was 80.16 months (95% CI, 28.80–49.65) in <5% and 39.22 months (95% CI, 28.80–49.65) in 5%≤ Ki-67 ($p = 0.004$).

Conclusions: The most important factors about the survival and prognosis of GIST are location, size, mitotic rate, Ki-67, necrosis and surgery status. Using tobacco/alcohol may be related to survival. This study should be further investigated with extensive data.

1. Introduction

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of the gastrointestinal tract. Since they originate from Cajal cells, a type of interstitial pacemaker cells on a charge of gastrointestinal motility, they can be anywhere in the GI tract. They are mostly in the stomach, followed by the small intestine.[1,2] In the USA, the incidence is 4000–6000 new cases per year (7–20/million case).[3] Even though some patients get diagnosis incidentally, some cases present as loud clinics as acute abdomen. They can be either benign or metastatic. GIST mostly metastasize to liver tissue.[4,5] Main prognostic factors include tumor size (cm), rate of mitosis (count of mitosis in 50 high power field [HPF]) and

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Peer review under responsibility of Turkish Society of Medical Oncology.

https://doi.org/10.1016/j.jons.2019.10.003

anatomic location of the mass. GIST in small intestine tends to be more malignant than stomach GIST, with the same size and mitotic count. Since all types of GIST have malignancy risk, it is useful to categorize patients for their clinicopathological risks. For this purpose, the Armed Forces Institute of Pathology (AFIP) criteria is used widely.[6] GIST tends to stain immunohistochemical markers like CD 117/c-kit 95%, CD 34 60–70% so these markers are used in diagnostics. Recent studies showed Ki-67 and DOG-1 stains also have an important role in the assessment of GIST.[1,2] Surgical resection is the most important treatment option in non-metastatic GIST.

The first molecular targeted drug option in GIST treatment is imatinib mesylate, a specific tyrosine kinase inhibitor which is a c-kit receptor. It is advised as adjuvant therapy for a minimum of 3 years in high risk (rate of mitosis >5, extra gastric localization, ruptured tumor, and large-sized mass) patients.[7,8] If there is a progression or relapse, the dose of imatinib is increased or sunitinib is used instead.[9] If there is resistance against both imatinib and sunitinib, regorafenib is used to keep the disease under control.[10]

There is a limited number of studies regarding GIST. In 2013, Seker et al. made a nine-centered study to evaluate GIST patients in Turkey between 2002 and 2009. In this study, factors affecting survival, prognosis and disease-free survival of GIST in Turkey were assessed.[11] In this multi-centered study, patients in the Thrace area were not included. We aim to provide for the literature by evaluating the clinicopathological features of the patients in our region and further improve our management of these patients.

2. Methodology

2.1. Clinicopathological variables

In this study, 68 patients referred to Trakya University Medical School Hospital between January 1997 and January 2015 that were diagnosed histopathologically as GIST were included. Data were extracted from the patients' files. Main demographic data such as age and sex were recorded and also use of alcohol and tobacco, complaints at presentation, existence of surgical intervention after diagnosis, medical treatments' type and duration, response to treatment, presence of relapse or progression, if progressed, time between the start of treatment and progression, occurrence of metastasis, if metastasized localization of metastasis and patients final state were taken into account.

Macroscopical (primary location, size, the sight of necrosis, ulceration, vascularization) and microscopical (mitotic count, CD 117 stain positivity, DOG-1, PDGFRA, CD 34, desmin, S-100, NSE, and Ki-67 index) data were extracted from pathology reports. Risk groups were recorded using AFIP criteria.

2.2. Statistical analysis

Evaluation of clinical and demographical features was made by using descriptive statistic methods. Survival calculations were made using the Kaplan-Meier method. Prognostically important factors like histopathological, clinical features and treatment options regarding survival rate were found with the log-rank test. Factors about relapse were researched with one-variable analysis. The relationship between non-parametric values was assessed with the chi-square test. Comparison between parametric groups was found with student test. SPSS 20 (license number 102406642) is used for statistical analysis. $p<0.05$ was chosen as statistically relevance.

3. Results

Sixty-eight patients were included in this study. The mean age for the patient group was 60.6 ± 10.6 (32–84). Thirty-seven of patients were male (54.4%) while the rest was female. In the Thrace region, the most common symptom was stomach pain (38.2%) while the most frequent presentation was small intestine (42.6%) followed by a gastric presentation (36.8%).

The most frequently seen immunohistochemical stain was CD 117 (76.5%). Forty-two patients' (61.8%) specimen stained CD 34 marker. Three patients' (4.4%) specimen stained positively desmin while 57 (83.8%) were negative. Ten patients' (14.7%) specimen stained positively S-100 while 46 (67.6%) were negative. Fifteen out of 17 patients whose specimen checked for DOG-1 stain were positive while 9 out of 9 patients (100%) had positively stained PDGFR.

Thirteen patients (19.1%) had metastasis. The main metastasized organ was the liver (84.6%) even though one patient had skin metastasis.

Patients in Thrace region were mostly in a high-risk category (57.4%) according to AFIP criteria while 8 (11.8%) had low, 6 (8.8%) had intermediate, 2 (2.9%) had very low risk. Three patients (4.4%) showed no risk.

Patients' mean Ki-67 index was 15.4 ± 15.2% (median 10%, min. 10%, max. 60%). The mean tumor size was 10.2 ± 5 cm (median 9.5 cm, min. 1 cm, max. 24 cm) while the mean count of mitosis was 18.3 (median 9.5, min. 0, max. 126) in 50 HPF.

Rate of relapse and metastasis was found elevated in bigger sized tumors. The mean tumor size with relapse was 11.8 ± 3.8 cm meanwhile it was 6.5 ± 3.0 cm in non-relapsed patients ($p = 0.01$). The mean size of the tumor was 13.5 ± 4.4 in the metastatic group although this data was 8.8 ± 4.7 cm in the non-metastatic group ($p = 0.01$). It was discovered that metastasis rates had no significant relation with mitotic rate and Ki-67 index. The same situation applies to relapse rates.

The mitotic rate and size of the tumor were greater in necrotic tumors. The mean mitosis count was 21.0 ± 3.6 in necrotic tumors and 7.2 ± 9.9 in non-necrotic tumors ($p = 0.005$). The mean size was 10.8 ± 5.0 cm in necrotic tumors and 5.6 ± 3.0 cm in non-necrotic tumors ($p = 0.009$). Ulceration in tumors had no significant relation with mitotic rate and tumor size. The same applies to the bleeding of tumors.

Overall survival was longer both in non-smoker and non-drinker patients. Median overall survival was 80.16 months in non-smoker group (95% CI, 27.83–132.49) and 24.64 months (95% CI, 15.49–33.78) in the smoker group ($p = 0.001$). The median overall survival was 80.09 months in the non-drinker group (95% CI, 13.99–146.20) and 24.64 months (95% CI, 13.18–36.10) in drinker group ($p = 0.05$).

Overall survival was longer in tumors located in the small intestine. Median overall survival was 41.39 months (95% CI, 28.57–54.21) in stomach localization and 80.09 months (95% CI, 7.25–152.94) in small intestine localization and 35.68 months (95% CI, 0.00–92.30) in colon localization ($p = 0.05$).

Surgery was also a factor that prolonged survival. Median overall survival was 80.09 months (95% CI, 0.00–170.73) in patients undergone surgery and 16.98 months (95% CI, ?-?) in patients had not been operated ($p = 0.001$) (Fig. 1).

Overall survival was longer in tumors which mitotic rate was <5/50 HPF. Median overall survival was 80.16 months in patients who had less than 5 mitosis and 39.22 months in higher mitotic rate (95% CI, 31.58–46.87) ($p = 0.034$) (Fig. 2).

Overall survival was longer in tumors with Ki-67 < 5%. Median overall survival was 80.16 months (95% CI, 28.80–49.65) in <5% and 39.22 months (95% CI, 28.80–49.65) in 5%≤ Ki-67 ($p = 0.004$) (Fig. 3).

Patients who had metastasis had a significantly shorter survival. Median overall survival was 24.64 months (95% CI, 0.00–54.40) in

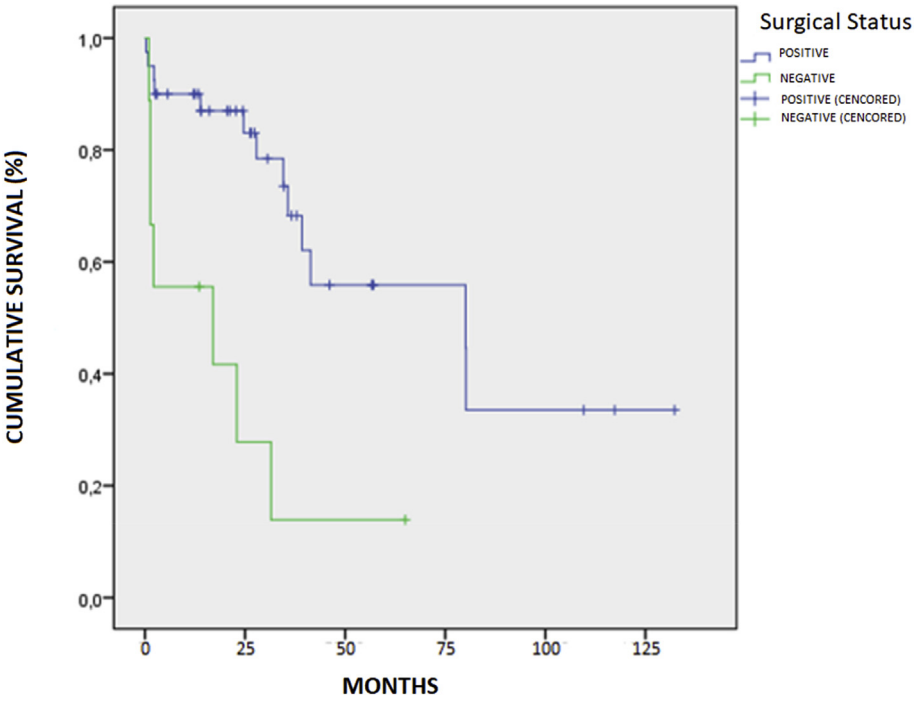

Fig. 1. Relation of Surgical Status and Survival in GIST patients.

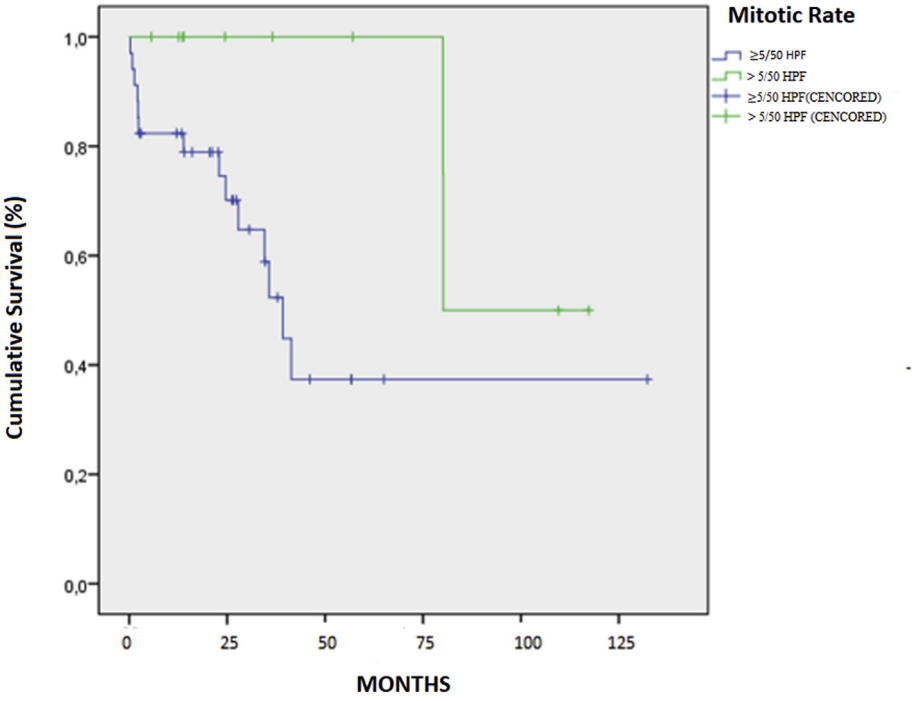

Fig. 2. Relation of mitotic rate and survival in GIST patients.

patients with metastatic tumor and 80.09 months (95% CI, ? = ?) in non-metastatic tumors (p = 0.005) (Fig. 4).

According to AFIP criteria, patients listed as the high-risk group had a significantly shorter overall survival compared to others. The high-risk group's median overall survival was 39.22 months (95% CI, 29.49–48.96) while others had a median of 80.16 months, 95% CI, ?-? (p = 0.15) (Fig. 5).

Patients were also evaluated by their type of treatment, their response to treatment and survival times. Thirty-two patients were assessed for adjuvant therapy, 13 (40.6%) had adjuvant imatinib therapy.

Median overall survival in adjuvant imatinib treatment group was 41.58 months (95% CI, 9.62–59.49) and 81.87 months (95% CI, 29.93–130.39) in untreated patients (p = 0.73).

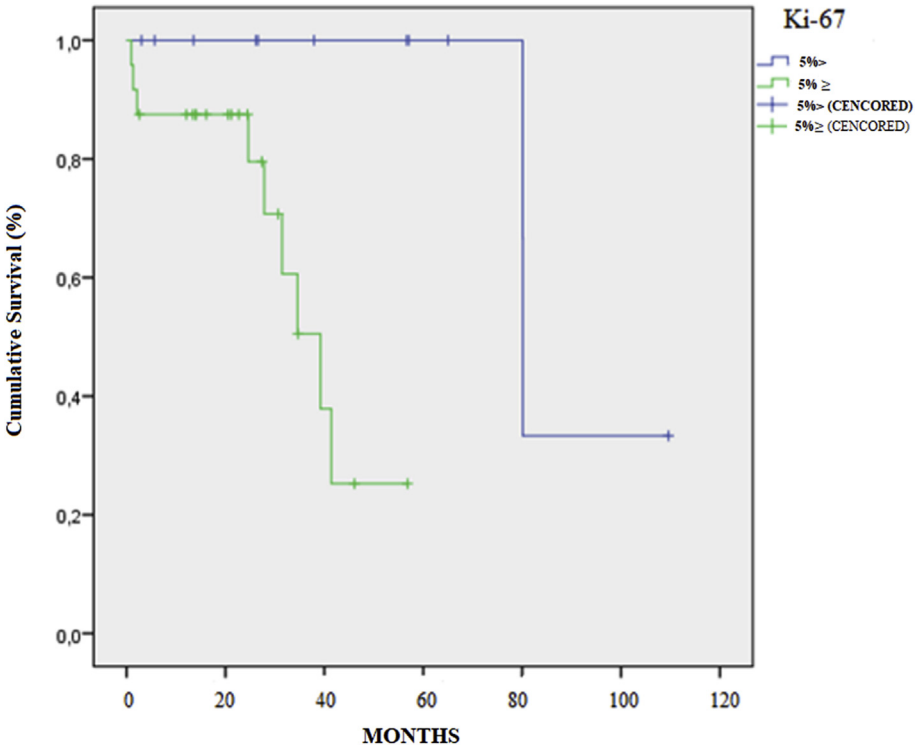

Fig. 3. Relation of Ki-67 index and survival in GIST patients.

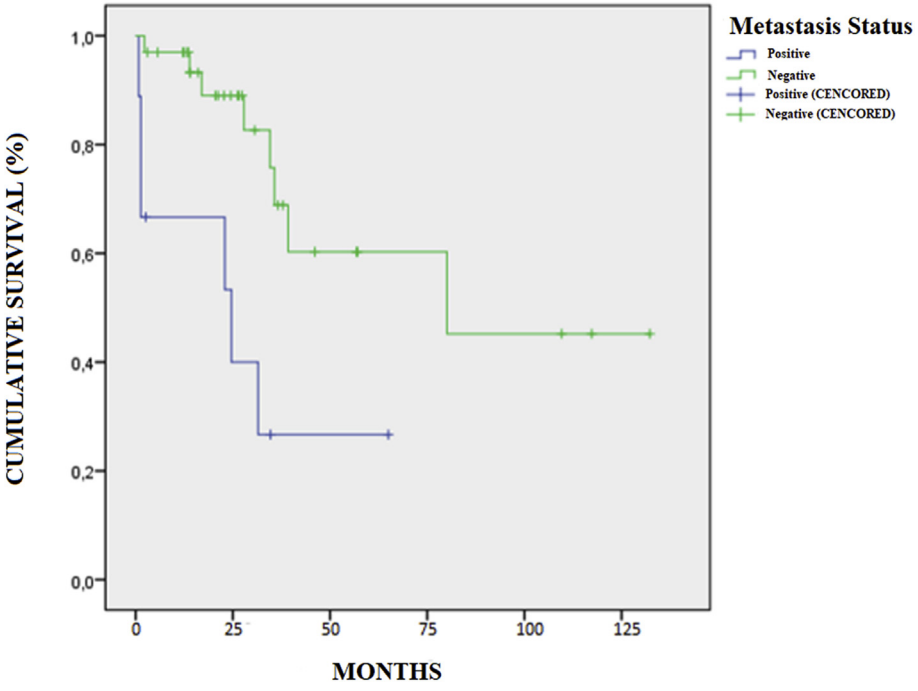

Fig. 4. Relation of Metastasis Status and survival in GIST patients.

Thirteen patients had imatinib therapy as an adjuvant. Two (15.4%) of them were relapsed. Two (25%) out of 8 patients who had a relapse had imatinib therapy, while the other six were followed up without treatment.

Median progression-free survival in patients who received imatinib for metastatic tumors was 11.2 months, while 5 months in sunitinib patients. No patients received regorafenib.

4. Discussion

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of the gastrointestinal tract. They develop under c-kit mutation. Clinical manifestations can be vastly variable. They can be diagnosed mostly 5th and 6th decade.[12] In this study, the mean age of patients was 60, parallel to literature. While the

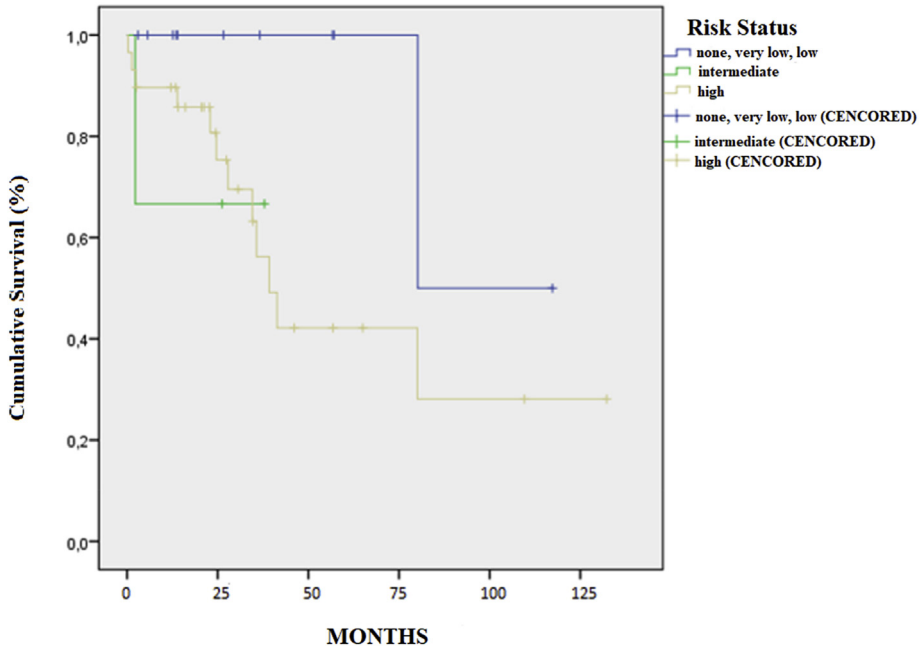

Fig. 5. Relation of Risk Status and Survival in GIST patients.

most common symptom is abdominal pain, they can be asymptomatic therefore incidentally diagnosed. Non-specific complaints about the gastrointestinal system like loss of appetite, fatigue, weight loss and bloating around the abdomen. Also, symptoms correlated to mortality and morbidity like intestinal obstruction, perforation, obstructive jaundice, and GIS bleeding can also be seen with these patients.[4,5] Most frequent complaint was abdominal pain in our study. Eleven (6 for GIS bleeding, 4 for intra-abdominal bleeding, one for ileus) patients had the diagnosis of GIST after surgical operations. Therefore, GIST should be kept in a list of differential diagnosis in patients having subclinical gastrointestinal symptoms.

Gastrointestinal stromal tumors mainly locate in the stomach (50–60%), followed by the small intestine (25–30%), colorectal area (5–15%) and esophagus (2%).[13,14] In this study primarily located zone was small intestine (42.6%), followed by the stomach (36.8%). This could be explained either by the shortage of patients or a different distribution of GIST anatomical locations in our region. Furthermore, tumors located in the small intestine area are harder to diagnose therefore it is possible these patients referred to our clinic. Further extensive research to explain anatomical localization of the tumor in the Thrace region and if so reason for this etiological difference should be explained.

Gastrointestinal stromal tumors mainly metastasize to the liver and peryton. Lung and bone metastasis are rarer.[13] Skeletal muscle metastasis was seen seldom in literature.[15] In this study metastatic areas were parallel to literature, while one patient had skin metastasis. Although they are observed rarely, atypical types of metastatic lesions can exist in GIST.

Immunohistochemical stains are used in mesenchymal tumors' differential diagnosis. Hirota et al. reported a 94% positivity of c-kit in GIST patients.[16] On the other hand, approximately 5% of GIST may not express c-kit. In this study, parallel to literature, most frequently positive immunohistochemical stain was c-kit while 8% of patients' tumors didn't express c-kit. Alternative immunohistochemical stains are both used and searched to identify tumors don't stain c-kit, the most recent one is DOG-1 marker. In research with 425 patients, Espinosa et al. reported DOG-1 to have both sensitivity and specificity for GIST, being positive for 87% of patients.[17] DOG-1 marker tested patients in our research, 15 out of 17 (88.2%) were positive. Size of the tumor, rate of mitosis and Ki-67 index were not found statistically relevant with DOG-1 marker. Other immunohistochemical stains for evaluating GIST are CD 34, desmin and S-100. CD 34 was positive in 60%–70% of patients in numerous researches.[1,4,18] In our study our patients, similar to the studies mentioned above, had a rate of 61.8% positive CD 34 stain. Similarities between this research and literature about pathological assessments show high efficiency for our center.

In 2012, Joensuu et al. described independent poor prognostic factors as; larger tumor size, higher mitotic rate, extra stomach localization, existence of rupture and male gender, in a research containing 920 GIST patients.[19] Miettinen et al., in their study with 1765 patients with stomach localized GIST, interestingly found that sizes >10 cm and lower mitotic rates are relatively good prognostic factors. In these patients' follow-ups for 5–15 years, only 12% of them had metastasized, therefore the size of the tumor was not found to directly affect malignancy.[20] In another study of 906 ileum and jejunum localized GIST, Miettinen et al. found tumor size and mitotic rate are directly about prognosis. While patients with tumor size <5 cm and mitotic rate ≤5/50 HPF had a rate of 3% metastasis, this rate elevated to 86% to tumor size >10 cm and mitotic rate >5/50 HPF.[21] In this study, tumor size is found statistically significant to the rate of relapse and metastasis ($p = 0.01$). In our findings, parallel to literature, patients with larger sized tumors not only can be metastatic in diagnosis but also can have metastases after the diagnosis.

In a study made in Northern China with 142 either metastatic or relapsed patients, tumor localization, size, mitotic rate, choice of treatment were found prognostically relevant ($p < 0.05$).[22] Multi varied survival analysis showed mitotic rate and treatment choice to be independent prognostic factors for metastatic or relapsed GIST patients. Interestingly; in our study, contrary to the study mentioned above, the mitotic rate was not observed relevant to relapse or metastasis. It should be noted that, parallel to literature, survival rate showed significant relevance to the mitotic rate. In 2018 Zheng et al. illustrated in a 246 high-risk patient study that;

necrosis of tumor and rate of mitosis were independent factors for survival rate and the optimal threshold must be 20/50 HPF.[23] Overall survival rate was found worse for the patients whose mitotic rate was above 20/50 HPF. In our study, patients were categorized into groups as mitotic rate <5/50 HPF and >5/50 HPF and parallel to literature survival for the lower mitotic group was longer.

Some studies find Ki-67 as a useful rate when assessing metastasis and recurrence risk in GIST.[24,25] Oliveira and Pannain in a 54-patient study that was published in 2015, reported that patients with Ki-67 ≥%5 are statistically relevant to poor prognosis ($p < 0.001$).[26] In our study, patients with Ki-67 < 5% had 80.16 months median overall survival while Ki-67 ≥ 5% group had a median of 39.2 months ($p = 0.004$).

It is a common opinion that necrosis in a tumor is related to the general proliferation rate of the tumor. GIST with most aggressive nature has been observed to have macroscopically necrotic areas.[27] Oliveira et al. reported necrosis at a poor prognostic value in their 54-patient study.[28] In our study, patients with necrotic tumors, had higher mitotic rates and larger sizes, while this data was found statistically relevant to survival. Patients with non-necrotic tumors had higher survival. This opinion is also supported by our study as well. Radiologically and macroscopically visual of necrosis can contribute to the management of GIST since this visual is related to high mitotic rate and large tumor size. We would like to state that due attention must be paid to the preoperative aggressiveness of the necrotic tumors in the management phase.

Gastric GIST generally tends to be a better prognosis than non-gastric ones.[29] Emory et al. reported survival rates to be highest in esophagus tumors while small intestine tumors to have the lowest rates.[30] The same study reported tumor localization to be an independent prognostic factor from age, mitotic rate, and tumor size. Nakamura et al. reported in an 80-case study that there was no significant survival difference between GIST in stomach and GIST in another localization.[31] In 2006, Bertolini et al. reported, parallel to the literature; in a group of 118 GIST patients, most frequent localization as stomach and only %7 to be malignant while omental/mesenterial and colorectal GIST to be rare and have a poor prognosis.[32] Furthermore, they proved a cause of dyspeptic symptoms and bleeding facilitated early diagnosis of gastric GIST, while omental and colorectal GIST have late diagnoses. Therefore non-gastric GIST becomes larger until diagnosis. Kukar et al. reported in a 2015 study, where 4411 GIST patients (29 esophageal, 2658 gastric, 1463 small intestine, 126 colon, and 135 rectum) were evaluated, in spite of less surgical resection esophageal GIST cases were similar to gastric GIST cases in survival rates, meanwhile colonic GIST were worse than rectal GIST in survival rates.[33] In our study small intestine GIST cases were found to be better than gastric GIST patients regarding survival rate. These findings may be caused by the scarcity of the patients. On the other hand, considering the more frequent amount of small intestine GIST in our region, different etiological and geographical factors may cause different prognosis of GIST.

There are only a limited amount of studies about the relation between GIST prognosis and tobacco and alcohol usage. Because of a cigarette being a powerful P450 (CYP 1A2) inhibitor, Erp et al. thought in 2008 that it can change imatinib's (a drug mostly metabolized by CYP 3A4 and minorly CYP 1A2) pharmacokinetics. They haven't reported about such an effect, although they found tobacco increased imatinib-related anemia (grade 2≤) and fatigue.[34] In our study, tobacco and alcohol usage was statistically relevant to survival. Even though the non-user group had significantly longer survival, this can be caused by their lesser comorbidity. On the other hand; it should be noted that the scarcity of patients hindered a multi-variable analysis. The effect of tobacco and alcohol should be researched with a larger patient group and multi-variable analysis.

The standard procedure for GIST is excision of tumor surgically, the margin being negative (R0 excision) and starting adjuvant imatinib therapy. Neo-adjuvant imatinib therapy before surgery is an option in tumors that can't be resected in negative margins or if surgery may result as major functional sequelae.[9] In our study 83.8% of patients had surgery, 54.5% being curative. Patients who have undergone surgery had longer survival than others. Surgery is especially good in non-metastatic diseases. Also, it can provide effective palliation for systematic treatments to work successfully in metastatic cases.

In a 2013 study conducted by Seker et al., 333 GIST patients in our country were included. In the study mentioned above, the median survival time of patients was 26 months (4–166 months) while 1-, 3-, and 5- year survival rate were %96.9, %85.8 and %78.5, respectively. Patients' 5-year disease-free survival rate was %40. Patients who had R0 excision had both significantly better 5-year survival rate and median survival rate than metastatic patients ($p = 0.04$).[11] In our similar findings, it was found that the presence of metastasis had a significant relation with survival. Metastatic patients had 24 months as median survival in comparison with 80 months median in non-metastatic patients ($p = 0.005$).

In 2019, Sakin et al. included 74 operated and non-metastatic GIST patients into their study. Contrary to our findings but parallel to literature, small intestine GIST were shown to have significantly lower disease-free survival rates than gastric GIST ($p = 0.004$).[35] Small intestine localization, high-risk score, c-kit positivity and having adjuvant treatment were found as the most important factors for disease-free survival rate.

In another study in 2019, Cavnar et al., 1000 patients who had surgery were categorized as either before imatinib permission for intermediate and high-risk GIST, or after the permission. The group that was able to get adjuvant imatinib therapy showed better general survival rate while the most important prognostic factor was found as tumor size under 10 cm.[36] In our study metastasis rate and relapse risk was elevated in larger tumors, parallel to this study. Two patients (25%) out of 8 relapsed under the adjuvant imatinib therapy while the other 6 (75%) were observed without treatment. There wasn't a statistically significant difference between patients treated with imatinib as an adjuvant and others caused by the limited number of the study group.

There are limits to this study. Firstly, not every patient had clinical follow-up data. Furthermore; patients were not diagnosed in oncology clinics since the primary treatment of non-metastatic GIST is surgery. As a result of that, they are often referred to in surgical clinics. Thus, some of our patients were followed up from surgical clinics. All these reasons cause limitations on archived data and the statistical study's sole source of information was this available data. Therefore, our study should be assessed while keeping these limitations in mind.

Similarities between our study and the literature about the numerical results and prognostic factors illustrate that the disciplines regarding this tumor manage both the diagnosis and treatment phases effectively, although there are only 4–5 patients refer to our clinic per year.

5. Conclusions

The most important factors about the survival and prognosis of GIST are location, size, mitotic rate, Ki-67, necrosis and surgery status. Using tobacco/alcohol may be related to survival. Necrosis may be an indication of prognosis since tumors with necrosis have a higher mitotic rate and larger tumor size. This study should be further investigated with more extensive data.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors declare no conflict of interest.

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