The Relationship of Clinicopathological Findings and PDGFR-β Expression With Tumor Recurrence in Gastrointestinal Stromal Tumors

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ABSTRACT

Background: *Considering the difficulty in predicting the biological behavior of gastrointestinal stromal tumors (GISTs) based on histological findings alone, genetic abnormalities have recently become an area of focus. Platelet-derived growth factor receptor (PDGFR), with 2 isoforms (α and β) is one of the mutations that play a role in the development of GIST. There are very little data determining the relationship of GIST with PDGFRβ which is associated with poor prognosis in other mesenchymal and epithelial tumors. In this study, we aimed to show the relationship between clinicopathological criteria and recurrence. We also wanted to evaluate the effect of PDGFRβ expression on recurrence and clinicopathological findings.*

Methods: *We evaluated 40 GIST patients retrospectively for detailed clinicopathological findings, postoperative immunohistochemical tumor markers (CD117, Ki67), and also for tumor recurrence. Immunohistochemical examination for PDGFRβ was performed for the all GIST cases.*

Results: *Tumor recurrence was related to male gender (P = .003), serosal localization (P = .004), surgical margins positivity (P = .001), risk group (P = .011), mitotic activity (P = .000), and Ki67 proliferation index (P = .000). PDGFRβ was not significantly associated with tumor recurrence (P = .277).*

Conclusion: *We can say that the most important parameters related with recurrence of GISTs are mitotic activity and the Ki67 proliferation index. The determination of the cut-off value of the Ki67 proliferation index as 13% instead of 10% would be much more specific and sensitive. Although PDGFRβ may be used for the diagnosis of GIST as an alternative for PDGFRα in cases with cKIT negativity, it is not an indicator of tumor recurrence as in other tumors.*

Keywords: *Gastrointestinal stromal tumors, mitotic activity, Ki67, PDGFRβ, recurrence*

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) derived from the multipotent precursor cells of Cajal are the most common mesenchymal tumors of the gastrointestinal (GI) tract.[1] Although they may arise throughout the entire GI tract, more than half of these tumors (60%) are located in the stomach.[1] These tumors, representing 1-3% of all GI malignancies, rarely exhibit life-threatening malignant biological behavior.[2] However, the heterogeneous clinical features and morphology of the tumor make it difficult to predict the prognosis; and these tumors cannot be considered as benign either. Therefore, it is vital to identify independent prognostic factors for the accurate risk classification. Several scales, such as Armed Forces Institute of Pathology (AFIP) and Nationel Institutes of Health (NIH) criteria are used to assess the recurrent and metastatic risk for GIST. The AFIP, developed by Miettinen and Lasota, estimates the risk for recurrence and metastasis based on tumor diameter and mitotic activity, varying according to tumor localization (stomach, jejunum/ileum, duodenum, and rectum).[3] It is debated that the AFIP classification is more efficient in determining malignant biological behavior than the NIH and modified NIH criteria.[4] Independently from these histological parameters, tumor necrosis and tumor rupture have become the prominent findings with prognostic significance in the recent years.[2,5]

However, it is hard to predict the biological behavior based on histological findings alone. The prognosis of the patients with GISTs may vary even though they have the same risk stratification. In this regard, studies have been

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focused on genetic abnormalities that play a role in tumor carcinogenesis and tumor progression. Several genetic abnormalities have been reported in the recent years, and 85% of those constitute the oncogenic mutation of the KIT tyrosine kinase gene. This mutation has recently drawn remarkable attention because it constitutes the targeted therapy known as tyrosine kinase inhibitors.[6] In addition, activating platelet-derived growth factor alpha receptor (PDGFRα) mutations have been identified by Heinrich ve Hirota in a small subset of GISTs with a ratio 5-7% of the cases lacking KIT mutations.[7,8]

Platelet-derived growth factor (PDGF) isoforms that stimulate growth, survival, and motility of cells, exert their cellular effects by binding to α and β- tyrosine kinase receptors (PDGFRα and PDGFRβ).[9] Despite molecular similarities, PDGFRα-mutant GISTs have features distinct from the KIT-mutant GISTs such as tendency to locate in the stomach, and sometimes the immunohistochemically negative expression of KIT (CD117), usually by the lower potential for malignancy.[1] Although the number of studies that have investigated the expression of PDGFRβ in GISTs are quite limited, the expression of this molecule has been reported, albeit in a small number of those studies.[10,11] PDGFRβ has been found associated with tumor progression and poor prognosis in many epithelial and mesenchymal tumors, excluding GISTs.[12-14]

Therefore, we have aimed to clarify whether there is any relationship between PDGFRβ expression and the prognostic or histological features of GISTs and the relationship with low malignancy potential, and similarly with PDGFRα as another isoform of the receptor, or whether it increases the recurrence risk, as with many other tumors. In this study, we have aimed to retrospectively review 40 GIST cases and evaluate the effect of PDGFRβ expression in those patients. In addition, we have assessed the clinicopathological data that may have an effect on recurrence and survival, to determine the approach that is available for the patient.

MAIN POINTS

- *Mitotic activity and Ki67 proliferation index are the most important parameters related with the recurrence of gastrointestinal stromal tumors (GISTs).*
- *A value as 13% can be used for the cut-off value of the Ki67 proliferation index.*
- *PDGFRβ can be used in the cases with c-KIT negativity as well as PDGFRα.*
- *There is no relationship between tumor outcome and PDGFRβ expression in GISTs.*
- *c-KIT should not be used as a prognostic significance in GISTs.*

MATERIALS AND METHODS

A retrospective cohort of all patients with GIST who underwent curative surgical resection from 2009 to 2020 was reviewed. The clinical, pathological, and survival data of 40 patients, such as age, gender, tumor localization, multifocality, surgical margin status, preoperative and postoperative serum markers, histopathological characteristics of the postoperative immunohistochemical tumor markers (CD117, Ki67), and tumor recurrence were analyzed retrospectively. Immunohistochemical examination for PDGFRβ was performed for the paraffin block which best represented the tumor. The patients with inaccessible clinical and pathological data, inadequate pathological specimens, suboptimal immunohistochemical expression of PDGFRβ, and those who could not be followed-up in terms of recurrence/survival were excluded from the study.

The routine pathologic assessment of tumors was performed by a single experienced pathologist with 3 formalin-fixed, paraffin-embedded tissue blocks per tumor. The histological subtype of the tumor was identified as spindle, epithelioid, or mixed (spindle+epithelioid). The presence of cellular atypia characterized by pronounced nuclear enlargement, hyperchromasia, and pleomorphism was detected. Cellularity was determined as low and high.[15] Tumor tissues were examined regarding the presence of additional components such as chondroid or rhabdoid differentiation and also the presence of lymphovascular invasion. Mitotic rates were re-counted in 5 mm^2 of tumor area (50 HPF (×40) (high-power fields). In addition, data on tumor diameter, surgical margins on specimen, tumor invasion depth, ulceration, and necrosis were obtained by reviewing pathological reports. The percentage of necrosis was additionally determined for the tumors with necrosis. Based on the AFIP criteria based on tumor diameter (≤2 cm, >2 to ≤5 cm, >5 to ≤10 cm, >10 cm) and mitotic rate (≤5/5 mm^2 and > 5/5 mm^2), and by taking into consideration tumor localization (gastric, duodenum, jejunum/ileum, rectum), tumor risk was classified as very low, low, medium, and high.

In addition to the macroscopic and microscopic findings, immunohistochemical expressions of CD117 and Ki67 were re-evaluated. We used the following criteria for the re-evaluation of CD117 expression according to the

extent of staining; 0-10% staining (negative), 10-50% staining (focal), and >50% staining (diffuse). The intensity of staining was semi-quantitatively classified as (+) mild, (++) moderate, and (+++) strong.[15] The Ki67 proliferation index was calculated by counting positive nuclear staining in 1000 cells.

Finally, PDGFRβ (D-6) concentration of 1 ml (1 : 50-500) Mouse Monoclonal Antibody was stained using the Ventana BenchMark XT (Ventana Medical Systems Inc.) procedure with the Streptavidin–Biotin indirect immunoperoxidase method on 4-μm-thick tumor sections obtained from the formalin-fixed paraffin blocks. The intensity of the immunostaining was graded as negative (no staining or <10% staining of the tumor cells), weak (1+), moderate (2+), or strong (3+). The tumors with 2+ or 3+ staining were considered to be positive, while other staining grades were accepted as negativ.[11]

Tumor localizations were detected by reviewing the pathology reports, esophagogastroduodenoscopy (EGD) results, and imaging findings (ultrasonography (USG) vs computer tomography (CT)). The gastric localizations of these tumors were classified as proximal, middle, and distal, according to the Japanese Classification of Gastric Carcinoma.[16] In addition, data on the biochemical markers at the preoperative and postoperative sixth months such as CEA, CA 19-9, hemoglobin and platelet levels, as well as the presence of a secondary tumor or a postoperative complication were obtained from the patients' archived files.

The patients routinely received follow-up visits at the postoperative 6th and 12th months. The follow-up assessment involved medical history, physical examination, and routine laboratory testing. After onset of the treatment, the patients were followed-up with CT, magnetic resonance imaging, or positron emission tomography (PET) with [^{18}F] fluoro-2-deoxy-D-glucose (FDG) at the postoperative sixth month.

Frequency analysis was used for the differences between quantitative and categorical parameters. The chi-square likelihood-ratio and chi-square tests were used for the differences between quantitative and categorical parameters. The Kolmogorov–Smirnov test was used to test the normality of the distribution of scale parameters. The independent samples *t*-test was used for normally distributed parameters, while the Mann–Whitney *U*-test was used for non-normally distributed parameters. ROC analysis was implemented to assess the diagnostic accuracy of Ki67 for recurrence groups. All statistical analysis was performed using SPSS 17.0 for Windows at a 95% confidence interval, with a statistical significance level of 0.05. A *P*-value less than .05 was considered to be statistically significant.

This study was approved by Zonguldak Bülent Ecevit University Noninvasive Clinical Human Studies Ethics Committee (Date: May 27, 2020; Approval Number: 2020/11).

RESULTS

All the histomorphological findings (including necrosis, presence of ulcer, tumor diameter, mitotic activity, histological subtypes, differentiation, presence of atypia, depth of invasion, lymphovascular invasion, and tumor cellularity), clinicopathological data (including age, gender, localization, presence of multiple tumors and secondary tumors, surgical margins, and complications) are summarized in Tables 1 and 2.

The ages of the study group participants, consisting of 15 (37.5%) female and 25 (62.5%) male patients, ranged between 29 and 83 years. The tumors were most commonly localized in the stomach, at 67.5%. Most of the gastric GISTs were located in the middle, according to the Japanese classification. The tumors were multiple in 6 patients and concurrently localized in the stomach, jejunum, and cecum.

Colon and bladder carcinomas accompanied the GIST in 3 patients and in 1 patient, respectively. The postoperative complications reported were bleeding, disseminated intravascular coagulation (DIC), abscess, infection, and hernia. However, none of the patients became exitus due to these complications.

The risk groups, determined according to tumor diameter, mitotic activity, and localization, have also been mentioned in the tables.

Clinicopathological data were also compared regarding tumor recurrence and patient survival, and the results have been mentioned in Tables 1 and 2. We noticed tumor recurrence in 8 patients (20%). All patients with recurrent tumors were male (P = .003). Positive surgical margins, depth of invasion, and risk groups were parameters

Table 1. Comparison of Tumor-Related Clinicopathological Features with Recurrence

	Without-Recurrence (n = 32; 80.0%)	With Recurrence (n = 8; 20.0%)	*P*
Age, mean ± SD	62.69 ± 11.42	52.25 ± 13.77	.032[a]
Gender, n (%)			**.003[b]**
Females	15 (46.9)	-	
Males	17 (53.1)	8 (100.0)	
Localization, n (%)			
Stomach (distal)	6 (18.8)	-	
Stomach (proximal)	6 (18.8)	2 (25.0)	
Stomach (middle)	10 (31.3)	3 (37.5)	
Jejunum	5 (15.6)	3 (37.5)	.269[b]
Ileum	3 (9.4)	-	
Duodenum	2 (6.3)	-	
Presence of necrosis, n (%)	11 (34.4)	5 (62.5)	.150[b]
Presence of ulceration, n (%)	7 (21.9)	3 (37.5)	.377[b]
Histological subtype, n (%)			
Spindle	24 (75.0)	6 (75.0)	
Epithelioid	3 (9.4)	1 (12.5)	.950[b]
Mix	5 (15.6)	1 (12.5)	
Differantiation, n (%)			
No	27 (84.4)	6 (75.0)	
Chondroid	3 (9.4)	1 (12.5)	.542[b]
Rabdoid	2 (6.2)	1 (12.5)	
Cellularity, n (%)			
Low	9 (28.1)	2 (25.0)	
Moderate	15 (46.9)	2 (25.0)	.366[b]
High	8 (25.0)	4 (50.0)	
Presence of atypia, n (%)	6 (18.8)	4 (50.0)	.083[b]
Depth of invasion, n (%)			
Muscularis propria	16 (50.0)	-	
Serosa	14 (43.8)	8 (100.0)	**.004[b]**
Submucosa	2 (6.3)	-	
Surgical margins, n (%)			
Negative	25 (78.1)	1 (12.5)	
Distal/proximal	1 (3.1)	3 (37.5)	**.001[b]**
Serosal	6 (18.8)	4 (50.0)	
Risk group, n (%)			
None	5 (15.6)	-	
Very low	4 (12.5)	-	
Low	6 (18.8)	-	**.011[b]**
Moderate	5 (15.6)	-	

Table 1. Comparison of Tumor-Related Clinicopathological Features with Recurrence (*Continued*)

	Without-Recurrence (n = 32; 80.0%)	With Recurrence (n = 8; 20.0%)	*P*
High	12 (37.5)	8 (100.0)	
Multiple tumor, n (%)			
Absence	27 (84.4)	7 (87.5)	.612[b]
Presence	5 (15.6)	1 (12.5)	
Second tumor, n (%)			
Absence	28 (87.5)	8 (100.0)	.388[b]
Presence	4 (12.5)	-	
Complication, n (%)			
Absence	27 (84.4)	7 (87.5)	.363[b]
Presence (infection, bleeding, abscess, DIC e.g.)	5 (15.6)	1 (12.5)	

*a, Independent samples *t*-Test; b, chi-square likelihood-ratio; c, Mann–Whitney *U*-Test.
NA, Not Applicable; SD: Standard Deviation.
P value < .05 was considered statistically significant.

that indicated a statistically significant correlation with recurrence.

We also found that the number of mitoses higher than 5 is more sensitive and specific. In Graphic 1, an ROC curve for mitosis is shown. The area under curve (AUC) for mitosis was 0.883, indicating that 88.3% is the diagnostic value of mitosis for recurrence. At a cut-off value of 5 for mitosis, it has a sensitivity of 100%, and a sensitivity of 71.9% regarding recurrence.

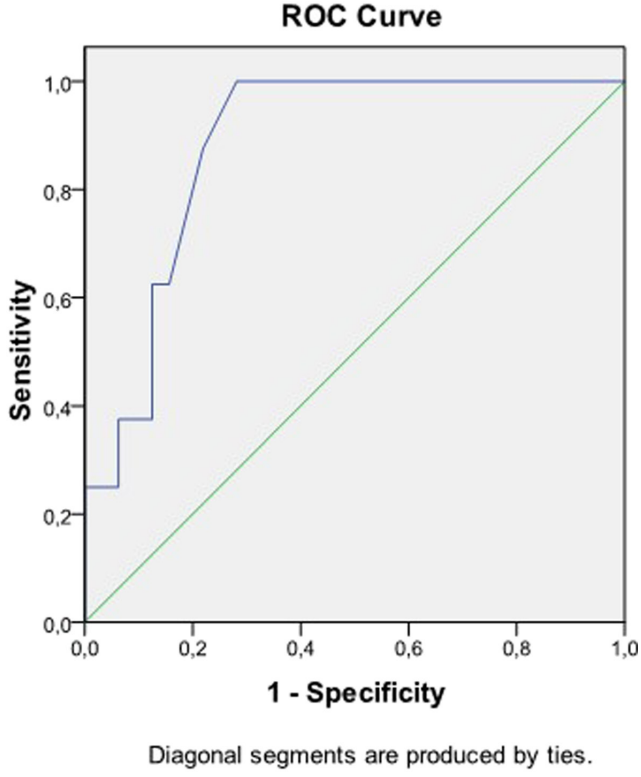
The evaluation of the patients in terms of survival revealed that disease-related death was detected in 15%. None of the deaths were caused by complications during surgery and most of deaths occurred after recurrence. Age was significantly higher in the group in which deaths occurred (66.67 ± 10.76) (*P* = .032). None of the other clinicopathological parameters had a significant effect on disease-related deaths (*P* > .005).

Table 2. Evaluation of the Relationship of Tumor Diameter and Mitotic Activity with Tumor Recurrence

	Without-Recurrence (n = 32; 80.0%)	With Recurrence (n = 8; 20.0%)	*P*-value
Tumor diameter mean±SD (cm)	7.79 ± 5.38	10.38 ± 3.34	.205[a]
Mitotic index mean±SD (HPF)	4.47 ± 4.56	25.63 ± 33.75	**.000**[c]

*a, Independent samples *t*-test; b, chi-square likelihood-ratio; c, Mann–Whitney *U*-test.
NA, Not Applicable; SD, Standard Deviation; HPF: High-power fields.
P value < .05 was considered statistically significant.

The relationship between immunohistochemical markers and tumor recurrence is summarized in Table 3. Ki67 was



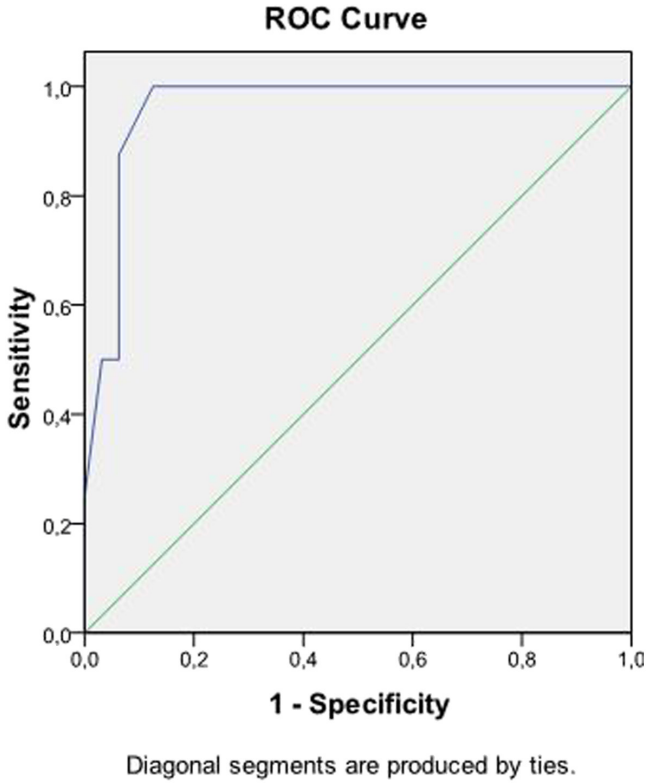
Graphic 1. ROC analysis result for mitosis in estimating recurrence.

Table 3. The Correlation of CD117, Ki67, and PDGFRβ Expression with Tumor Recurrence

	Without Recurrence (n = 32; 80.0%)	With Recurrence (n = 8; 20.0%)	*P*-value
CD117, n (%)			
Diffuse/Strong	28 (87.5)	6 (75.0)	.401[b]
Focal/Weak	4 (12.5)	2 (25.0)	
Ki67, mean±SD	5.28 ± 6.98	31.25 ± 20.83	**.000**[c]
PDGFRβ, n (%)			.277[b]
Negative	26 (81.25)	5 (62.5)	
Positive	6 (18.75)	3 (37.5)	

*a, Independent samples *t*-test; b, chi-square likelihood-ratio; c, Mann–Whitney *U*-test.
NA, not applicable; SD, standard deviation.
P value < .05 was considered statistically significant.

found to be a highly sensitive and specific marker in recurrence estimation. Different values of Ki67 proliferation index were determined (Figure 3). The high sensitivity and specificity of Ki67 in the recurrence estimation is shown by the ROC curve in Graphic 2. The AUC for Ki67 was 0.961, indicating that Ki67 has a diagnostic value of 96.1% for recurrence. Ki67 has a sensitivity of 100% and specificity of 87.5% at a cut-off value of 13.



Graphic 2. ROC curve for Ki67 proliferation index in estimating tumor recurrence.

The relationship between tumor characteristics and PDGFRβ expression is summarized in Table 4. We encountered positive expression with PDGFRβ in 9 tumors, and as expected, weak and focal staining was mostly observed with CD117 (*P* = .000). Regarding PDGFRβ expression, tumor recurrence and disease-related death indicated no statistically significant correlation (*P* = .277 and *P* = .702, respectively).

DISCUSSION

In parallel with the introduction of patient-tailored targeted treatment for GISTs, identification of the independent prognostic risk factors has become vital. These factors have also gained importance regarding a better

Table 4. Evaluation of the Relationship Between Tumor Characteristics and PDGFRβ Expression

	PDFGRβ Negativity (n = 31; 77.5%)	PDFGRβ Positivity (n = 9; 22.5%)	*P*-value
Ki67, mean±SD	9.68 ± 15.44	13.22 ± 14.23	.483[a]
CD117, n (%)			
Diffuse/Strong	31 (100.0)	3 (33.3)	**.000**[b]
Focal/Weak	-	6 (66.7)	
Tumor diameter, mean±SD	7.44 ± 4.68	11.31 ± 5.64	**.044**[c]
Mitosis, mean±SD	8.03 ± 17.67	11.00 ± 16.03	.444[a]
Localization, n (%)			
Stomach (distal)	4 (12.9)	2 (22.2)	
Stomach (proximal)	6 (19.4)	2 (22.2)	.511[b]
Stomach (middle)	11 (35.5)	2 (22.2)	
Jejunum	5 (16.1)	3 (33.3)	
Ileum	3 (9.7)	-	
Duodenum	2 (6.5)	-	
Cell component, n (%)			
Spindle	27 (87.1)	3 (33.3)	
Epitheloid	1 (3.2)	3 (33.3)	**.006**[b]
Mix	3 (9.7)	3 (33.3)	
Atypia, n (%)	4 (12.9)	6 (66.7)	**.002**[b]

*a, Independent samples t-test; b, chi-square likelihood ratio; c, Mann–Whitney *U*-test.
NA, not applicable; SD, standard deviation.
P value < .05 was considered statistically significant.

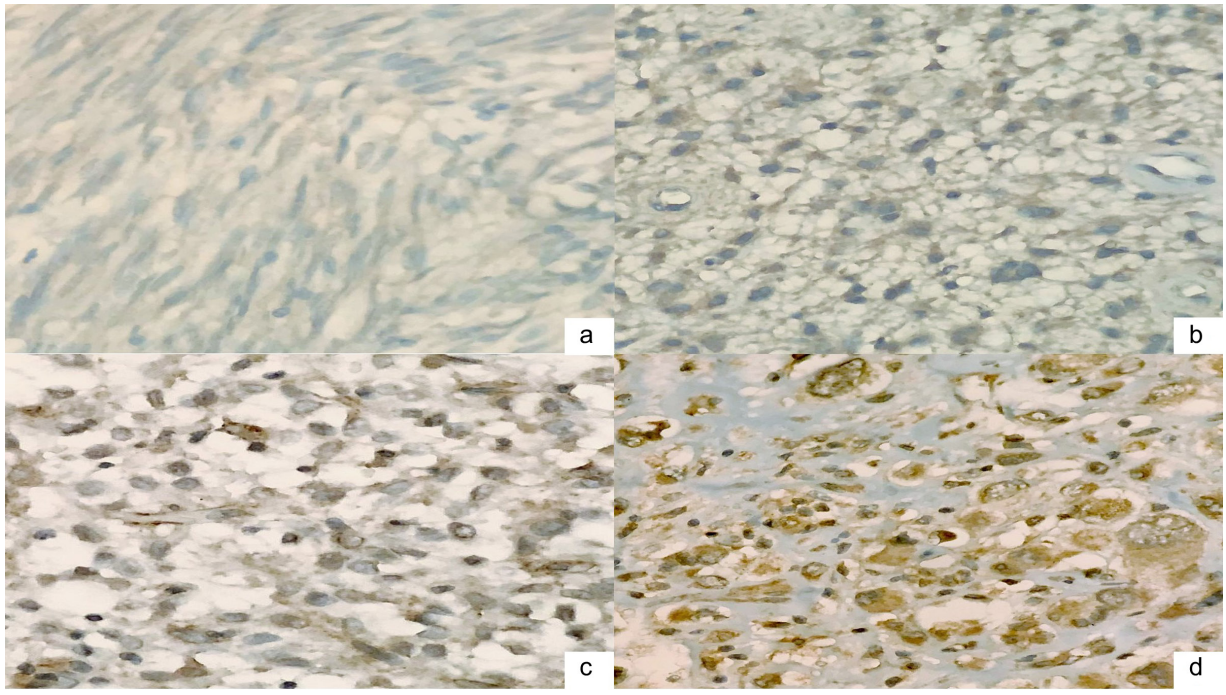


Figure 1. Evaluation of PDGFRβ immunohistochemical expression. (a) no staining in tumor cells (grade 0) (×400); b) mild PDGFRβ expression graded as 1 (×400); (c) grade 2 moderate PDGFRβ expression considered as positive staining (×400); (d) strong expression with PDGFRβ considered as positive staining (×400).

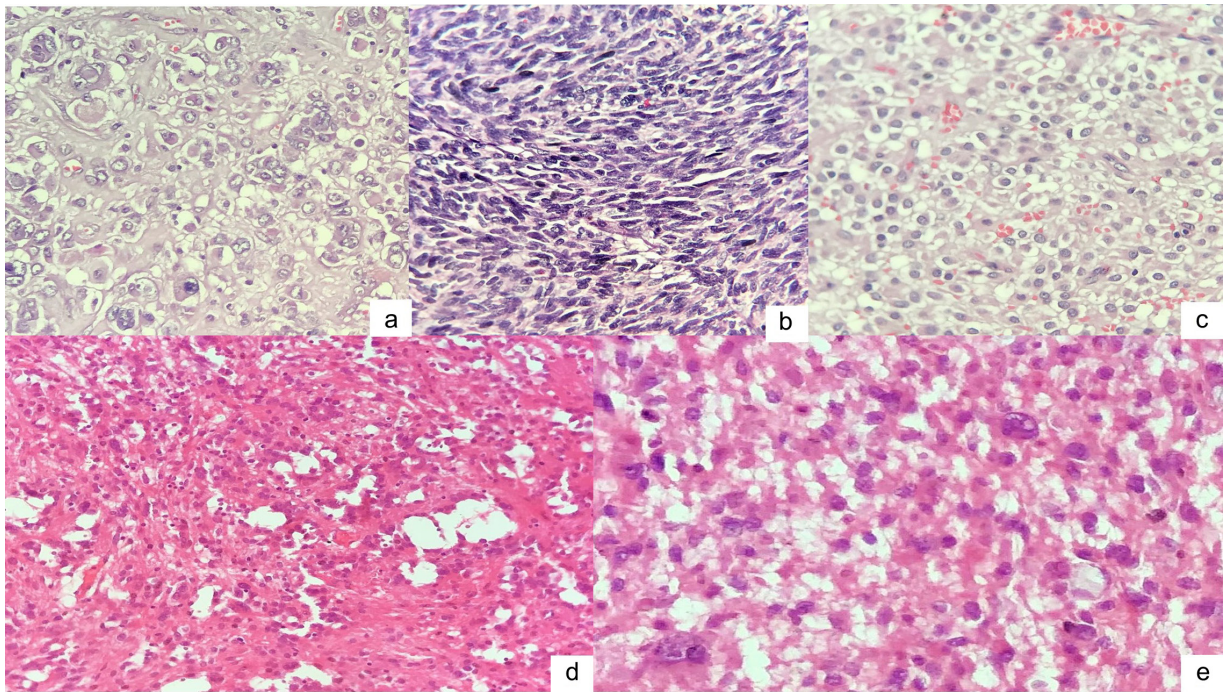


Figure 2. Different histological patterns and features of GIST. (a) Rhabdoid differentiation of GIST (HE, ×400); (b) GIST with spindle cell morphology and high cellularity (HE, ×400); (c) GIST with epitheloid cell morphology (HE, ×400); (d) GIST having vascular like pattern (HE, ×200); (e) Tumor cells with significant pleomorphism and atypia (HE, ×400).

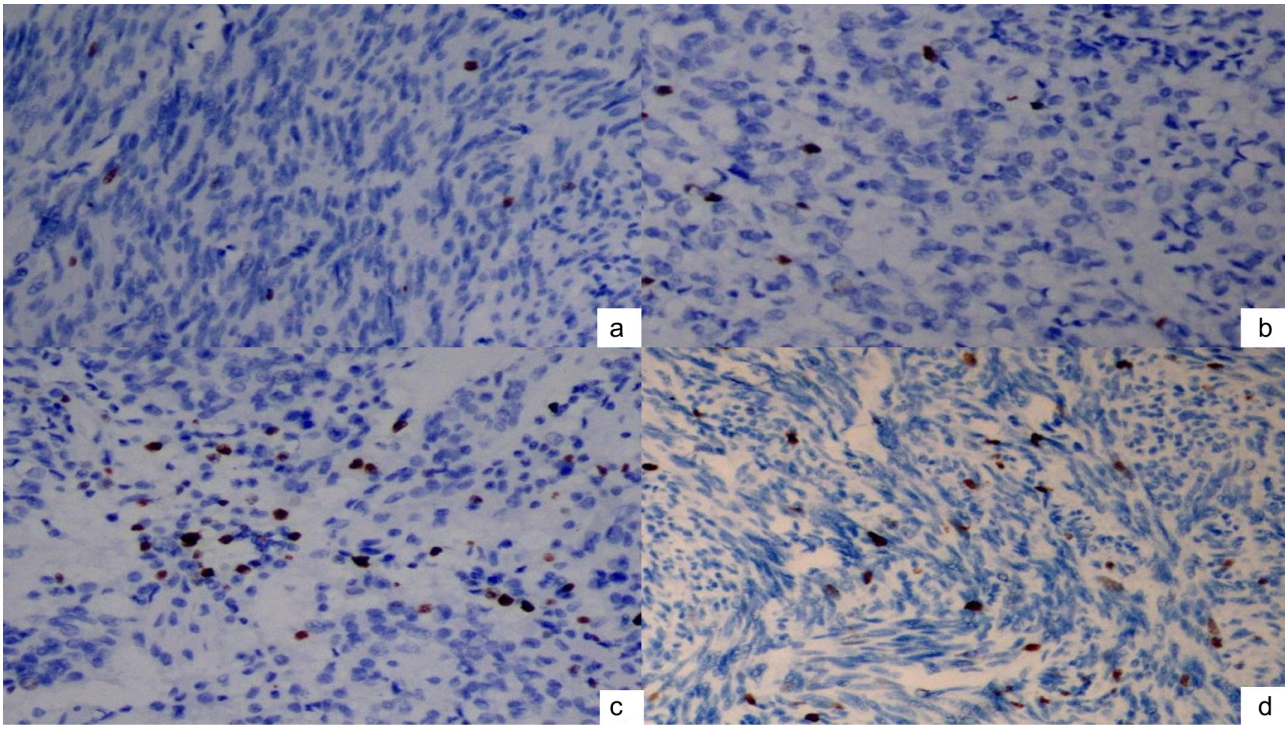


Figure 3. Ki67 proliferation index. (a) Low proliferation index as 1-2% with Ki67 (×200); (b) 3-4% Ki67 prolifetion index; (c) Relatively high proliferation index (×200); (d) High proliferation index as 12-13% (×200).

and more accurate risk classification of GISTs for more accurate postoperative follow-up strategies. In the present study, we assessed histopathological and clinical parameters of 40 patients diagnosed with GIST during surgery. We also evaluated the role and prognostic significance of PDGFRβ in diagnosis of GIST.

A recent review of the records in the Surveillance, Epidemiology, and End Results database including 2537 patients with GIST revealed that age over 65 years is a negative prognostic risk factor.[17] Interestingly, in our study, patients with recurrent tumors were younger, but these data were not statistcally significant. A statistically significant difference was encountered in terms of male gender, among the patients with recurrence.

In this study, the rate of gastric localization was 68.9%, parallel to the literature.[18] In many studies, it has been suggested that gastric GISTs generally tend to have better prognosis.[19] We have identified no significant correlation of tumor localization with aggressive pathologic characteristics and poor outcome.

In our study, 50% of the tumors belonged to the high-risk group according to AFIP. This result was correlated to data from Turkey, including a 29-center and a 3-center study.[20,21] In a research including 920 GIST patients, Joensuu et al. have defined larger tumor size, higher mitotic rate, extra-gastric localization, tumor rupture, and also male gender as the independent prognostic factors.[22] We agreed to determine the gender as a risk factor. We have also found that recurrent GISTs were in the high-risk group, parallel to the literature. Although mitotic activity was the parameter which increased the recurrence rate, tumor diameter was not found correlated with recurrence for any localization in our study. In fact, this result of our study was not surprising. Miettinen et al have suggested that tumor diameter was not associated with malignant behavior in gastric-localized GISTs; however, it was a poor prognostic factor for tumors localized in the ileum and jejunum.[23,24] Similar to our study, Supsamutchai et al have found that the recurrence rate does not show a statistical significance for every size of tumor independent of mitotic count.[2] It is possible to say that tumor diameter may be prognostic if it is correlated with tumor localization. According to AFIP criteria, developed by Miettinen et al, >5/50 HPF mitotic activity has been found statistically significantly correlated with the rate of relapse and metastasis.[3] Supsamutcahi et al have interestingly suggested that mitotic index count more

than 6 HPF is more significant regarding recurrence.[2] We can say that mitoses at a cut-off value of 5 have 100.0% sensitivity and 71.9% specificity according to our data.

Yi et al have estimated that patients with GIST accompanied with tumor necrosis carry an approximateley 7-fold increased risk for disease progression and a 4-fold increased risk for recurrence.[25] However, data on the relationship between tumor necrosis and prognosis are inconclusive. We did not find any significant relationship between tumor necrosis and tumor recurrence.

Three morphological subtypes have been defined for GISTs according to WHO classification, such as spindle (70%), epiteloid (20%), and mixed (10%) subtypes.[26] In our study, spindle morphology was dominant in 75% of the tumors, in parallel with WHO data.

Many histological criteria have been determined in the predictive prognosis of GIST. However, none of those could be concluded. Our study is one of the rare studies in which histological criteria were examined in such comprehensive detail. We can say only cellular atypia was significantly correlated with tumor recurrence, similar to data from Guler et al[15] However, we can suggest, according to our results, that histological criteria may not be very helpful in predicting tumor prognosis. We believe that this result is the consequence of the subjectiveness of histological criteria.

Increased depth of tumor invasion, and consequently the pathological stage, and clean surgical margins are among the most important criteria that may negatively affect the tumor prognosis. For this reason, it was not surprising that tumor recurrence was detected in GISTs with serosal localizations and positive surgical margins in our study.

Many authors have suggested that immunohistochemical studies performed to analyze the proliferation index should present a much more objective approach in the prediction of recurrence. In the recent studies, a Ki67 proliferation index over 10% has been accepted as an important prognostic factor.[27,28] Similarly, we have considered the Ki67 proliferation index as the most specific and sensitive prognostic marker. According to our data, we believe that a cut-off value of 13% instead of 10% may be much more specific and sensitive.

Immunohistochemical staining of c-Kit, CD34, SMA, S100, and DOG-1 is necessary for the accurate diagnosis of GISTs and differential diagnosis.[18] Miettinan et al have demonstrated strong diffuse positivity of cKIT and CD34 at the rates of 91% and 82% in the gastric GIST cases, respectively.[23] Similarly, 85% of the tumors showed diffuse and strong expression with CD117 in our series. However, the relationship between immunohistochemical markers and prognosis is not clear. Recently, Kang et al suggested that c-Kit and DOG-1 negativity might be potential prognostic factors for poor outcome in GISTs.[29] On the other hand, Liu et al have debated in their series of 2570 cases that previously mentioned immunohistochemical markers may play an important role in the diagnosis of GIST. However, their prognostic significance level is limited.[30] In the light of our data, it is not possible to say that c-KIT has a prognostic significance.

It is known that PDGFRα plays a role in the accurate diagnosis and also in the differential diagnosis of c-KIT-negative GISTs.[11] However, there are not many studies that have evaluated the expression of PDGFRβ in GISTs. It would not be surprising to expect similar expression patterns for receptors α and β which are 2 different isoforms of PDGFR, a type 3 tyrosine kinase receptor.

The fact that McCarthy et al have suggested the upregulation of PDGF-B resulting in metachronous gastrointestinal stromal tumor and dermatofibrosarcoma protuberans oriented us to consider PDGFRβ expression in GIST cases.[10] We also aimed to evaluate the prognostic significance of PDGFRβ because of its presentation as an indicator of tumor recurrence and adverse course in many cancers such as colon and prostate cancer as well as mesenchymal tumors, except GIST.[12-14]

However, PDGFRα-mutant GISTs are expected to have a lower potential of malignancy, in addition to features such as a striking predilection for the stomach and various expressions of c-KIT.[1]

Based on this contradiction about PDGFR, we compared PDGFRβ expression in terms of tumor histological and prognostic criteria in our study. We also investigated the relationship between PDGFRβ expression and tumor recurrence. Similar to PDGFRα, PDGFRβ positivity was significiantly associated with c-KIT negativity. The data have supported the premise that both receptors show similar expression patterns in GIST cases. According to our study, it is not possible to say that there is a negative correlation between PDGFRβ and tumor prognosis similar to other tumors, or to suggest a positive relationship similar to the relationship between PDGFRα and GIST.

We may conclude that PDGFRβ is not associated with tumor recurrence in GISTs.

There are limitations of our study. First, our study was retrospective and some of the data were based on the information obtained from the patient files. The other limitation was the subjectivity of the histological parameters. Although we have attempted to present objectivity based on previous studies for histological criteria, we consider that an evaluation as mild, moderate, or severe may vary from person to person. However, we think that this limitation about subjectivity is not unique to our study. Finally, it was not possible to evaluate histological criteria absoultely independent of the other criteria because they were commonly accompanied by others.

Thus, we can say that the most important parameters related to the recurrence of GISTs are mitotic activity and the Ki67 proliferation index. The determination of the cut-off value of the Ki67 proliferation index as 13% instead of 10% would be much more specific and sensitive. The assignment of risk groups according to AFIP criteria is very crucial in estimation of the recurrence risk. However, mitotic activity has a more critical role than tumor diameter in assignment of risk groups. We have found no relationship between tumor outcome and PDGFRβ expression similar to non-GIST tumors. However, PDGFRβ can be used in the cases with c-KIT negativity as well as PDGFRα, since PDGFRβ exhibits the same expression pattern as PDGFRα in the immunohistochemical staining processs.

Despite these limitations and the limited number of cases, we strongly believe that our study will provide an important contribution to the studies in this field. Our study may be helpful in clarification of the uncertainty regarding the use of histological criteria as prognostic markers. We expect that the results of our study will shed light on GIST literature even though further comprehensive prospective trials are needed on this subject.

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