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Original Article

Diagnostic and prognostic roles of DOG1 and Ki-67, in GIST patients with localized or advanced/metastatic disease

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Abstract: Aim: Gastrointestinal stromal tumor is the most common mesenchymal neoplasia in the gastrointestinal tract and has a broad spectrum of pathological patterns and also clinical features changing from benign to malignant. Although the well-characterized parameters to predict the outcome have been the size and the mitotic index of the tumor in the patients with early-staged disease, bulky recurrent or metastatic tumor, resistance to medical treatment and mutation analysis are the prognostic factors for advanced stage-GIST. The aim of this study is to investigate new and more practical tissue markers, such as DOG1 and Ki-67 to specify the GIST diagnosis and also to predict the outcome in GIST patients with both localized and advanced staged disease. Methods: For the last 14 years, from 1999 to 2013, 111 patients with a histopathological GIST diagnosis from the hospital files were enrolled to the study. In their parafin-embedded tissue samples, DOG1 and Ki-67 expressions were evaluated with immunohistochemisty by two independent pathologists from Cukurova University Medical Faculty. Patients were divided into two groups, the patients with localized disease treated by surgery and the patients with advanced/metastatic disease. DOG1 and Ki-67 expressions were corelated with other diagnostic and prognostic histopathological markers and also the clinical outcome in these two group of patients. Results: The specificity and the sensitivity of DOG1 in GIST diagnosis was found 94 and 43%, respectively. DOG1 expression was especially important in the diagnosis of c-kit negative cases. Although Ki-67 was not found a statistically significant prognostic factor for overall survival, it was strongly corelated with mitotic index which is a well-known standart prognostic factor for localized disease. Discussion: DOG1 seems to be an important diagnostic tool for clinically suspected GIST diagnosis in both advanced or early staged patients whose tumours are c-kit expression negative. On the other hand, Ki-67 can be a stronger candidate for prognostic factor instead of mitotic index to identify the proliferative cells out of mitotic phase but this statement needs be prospectively validated on studies with large number of patients.

Keywords: Gastrointestinal stromal tumor, prognostic factor, Ki-67, DOG1

Introduction

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumor of the gastrointestinal tract and it originates from the interstitial Cajal cells (ICC) in normal bowel wall or from precursors neoplastic of these cells [1]. GIST cover 5% to 10% of all sarcomas. Approximately 25% of all GIST are malignant. These tumors have been described that; they most common seen in ages 50-60, most often in the stomach even though all may take place in all regions of the gastrointestinal tract also in omentum, peritoneum, retroperitoneum and gallbladder [2, 3].

The most important in predicting tumor behavior morphological criteria, tumor diameter (cm maximum tumor diameter) and is mitotic rate. (mitosis number/50 BBA) İn GIST CD117 (c-kit protein) is detected immunohistochemically in almost 98-100% of all cases. CD-34 which related with generally hematopoietic and vascular endothelial cells also detected as 72 to 78%

of GIST, the smooth muscle actin (SMA) is 20 to 40% positiveness; S-100% is with 6-28% positiveness, desmin determined with 4-5% positiveness [1, 2]. However, despite all these diagnostic markers diagnostic difficulties being drawn in some cases and the new tissue markers with high sensitivity and specificity are needed. In recent years, together with histopathological examination of gene expression and of DOG1 positivity both gained importance in determining diagnosis and prognosis. There are publications suggest that DOG1 is more specific and sensitive for the diagnosis of GIST than CD117 [4, 5].

In recent years new systems are investigated like the "recurrence risk scoring" is that shows targeted agents which will be useful in patients. Several studies of Ki-67 in predicting the malignant potential of GISTs is said to be helpful [6, 7]. Some authors think that mitotic index reflects the M phase of mitosis only; but Ki-67 also defines proliferation of cells in G1, S, G2 phases and therefore can be used as an objective criterion in the evaluation of GIST malignancy [8]. In recent years; when Ki-67 labeling index is over 10% it is reported as significantly worse prognostic value [8-10]. The aim of this study is to investigate new and more practical tissue markers, such as DOG1 and Ki-67 to specify the GIST diagnosis and also to predict the outcome in GIST patients with both localized and advanced staged disease.

Materials and methods

In our study 111 patients were included, from hospital data from 1999 to 2013 with a diagnosis histopathologically as GIST in last 14 years. DOG1 and Ki-67 expression was assessed immunohistochemically by two different pathologists from paraffin block samples of patients. Patients were divided into two groups one group was with localized disease after surgery and other group was with advanced or metastatic disease. ki-67 and DOG1 expression in both groups were compared according to diagnostic and prognostic histopathologic markers and clinical outcome. demographic factors, symptoms, clinical findings, surgical operations, residential area of the tumor, metastasis assets/If settlement, recurrence, and histopathologic findings of tumor tissue of patients were recorded. Patients according to age; Age below 50 years, 50-60 years and above 60 years were grouped to be. Tumor enclave were classified as gastric and non gastric tumors.

The tumor size, location, hemorrhage, necrosis, ulceration, or absence of lymph node metastases as macroscopic; number of mitosis as microscopic, histological subtypes were paying attention. Tumor diameter were grouped as ≤ 2 cm, 2-5 cm, 5-10 cm, > 10 cm. Mitotic count was assessed in 50 BBA and were classified as < 5, 5-10, > 10. Early stage patients, they were evaluated according to the tumor size and mitotic count up to 2002 the NIH consensus and were classified as very low risk, low risk, medium risk, high risk. The number of patients were less therefore the low-risk and low-risk were considered as a one group. Immunohistochemically desmin, c-kit, Ki-67, SMA, S-100, CD-34, DOG1 were evaluated. Ki-67-positive patients were divided into groups as under and over 10%. DOG1 positivity was evaluated as weak staining +1, moderate staining +2, strong staining +3.

Statistical analysis

SPSS version 19 was used to analyze the data. According to clinical and demographic characteristics the patients are summarized. to summarize mean ± SS and percentage was used. in the analysis of Univarit Kaplan Meir estimation method was used; each factor that affect the rate of life (age, stage, DOG1, Ki-67, risk groups, tumor enclave, mitotic index, tumor diameter) were examined and life distributions were compared with log-rank test. same methods was used to determine Factors affecting recurrence free interval time. In Multivariate analysis Cox regression was made to analyze and The effects of the factors used in the analysis of univarit were also detected in assay simultaneously. Significance level was $p < 0.05$ and under and they were considered as important contributory factor in prognosis.

Diagnostic and prognostic significance of c-kit, DOG1, Ki-67, mitotic index, SMA, S-100, desmin, CD34, were correlated with each other in cross tables.

İmmuohistochemical staining

In the study group of patients whom sections prepared from the paraffin blocks, Ventana brand BenchMark XT model automatic immu-

Table 1. DOG1 relationship with other parameters

Varables		DOG1 n (%)		*P* value
		Positive	Negative	
c-kit	positive	64 (90.1)	7 (9.9)	0.041
	negative	4 (57.1)	3 (42.9)	
CD34	positive	51 (89.5)	6 (10.5)	0.260
	negative	17 (81.0)	4 (19.0)	
SMA	positive	50 (87.7)	7 (12.3)	0.540
	negative	18 (85.7)	3 (14.3)	
S-100	positive	55 (88.7)	7 (11.3)	0.334
	negative	13 (81.3)	3 (18.7)	
KÝ-67	positive	59 (86.8)	9 (13.2)	0.623
	negative	9 (90.0)	1 (10.0)	
Desmin	positive	10 (100.0)	10 (100.0)	0.231
	negative	58 (85.3)	58 (85.3)	
Mitosis number	< 5	33 (90.1)	4 (40)	0.32
	5-10	19 (90.1)	5 (50)	
	> 10	16 (90.1)	1 (10)	
Tumor size	< 2 cm	13 (90.1)	1 (10)	0.62
	2-5 cm	14 (90.1)	3 (30)	
	5-10 cm	25 (90.1)	4 (40)	
	> 10 cm	16 (90.1)	2 (20)	
Location	gastric	27 (90.1)	4 (40)	0.060
	Non-gastric	41 (90.1)	6 (60)	
Early stage		52 (90.1)	8 (80)	0.58
Advanced stage		16 (90.1)	2 (20)	
Low risk		21 (90.1)	4 (40)	0.786
Mid-risk		12 (90.1)	2 (20)	
High-risk		35 (90.1)	4 (40)	
Ýncidentally	yes	9 (90.1)	0 (0.0)	0.27
	No	59 (90.1)	10 (100.0)	
Recurrence	yes	10 (90.1)	1 (10)	0.57
	No	58 (90.1)	9 (90)	
Metastasis	yes	9 (90.1)	1 (10)	0.62
	no	59 (90.1)	9 (90)	

nohistochemistry staining equipment BASIC AEC Detection kit (Ventana 5266041-760-020) and rabbit anti-human DOG1 polyclonal antibody (Spring Bio Science, E16711 RTU) and Monoclonal Mouse Anti-Human Ki-67 antigen was performed. Ki-67 (Dako M7240), 1/150 dilution was applied.

Results

In the study there was 53 (47.7%) male and 58 (42.3%) women; The median age was 58 ± 13.3 (11-83), including a total of 111 patients. The most common complaints of was vague abdominal pain (60%). Other rare causes among applicants were gastrointestinal bleeding and fatigue. 111 patients had pre-diagnosis with upper gastrointestinal endoscopy and abdominal CT. GIST incidentally detected in 11 (9.9%) patients whom taken to operation because of other reasons. Three patients had been operated due to ileus. All patients underwent radical surgery in the direction of oncological principles. 77 (69.4%) patients were given postoperative imatinib therapy. In three patients that developed resistance to imatinib treatment sunitib was given. Tumors were located in 41 (36.9%) patients at stomach, in 48 (43.3%) patients at intestine. Colon, omentum, esophagus, retroperitoneum were other common residential areas. 97 (87.4%) patients, while there were no distant metastases, 14 (12.6%) patients had metastasis. The most common site of metastases were liver in 11 (78.6%) patients. Other metastatic areas were ovarian and bladder. 1 (9%) patient had both liver and lung metastases. While 8 patients had metastases at diagnosis 3 of patients had metastasisi at recurrences and metastases were present in 4 patients without the recurrence. During the follow up Disease had recurred in 13 (11.7%) patients, although 98 (88.3%) patients had no recurrence. Histopathological examination of tumors 87 (78.4%) patients had spindle, 16 (14.4%) patients had mixed type, 8 (7.2%) patients had epithelioid cell character. The number of cases with tumor diameter ≤ 2 cm was 15 (13.5%), 2-5 cm with 23 (20.7%) cases, 5-10 cm with 47 (42.3%) cases, > 10 cm, with 26 (23.4%) cases. The median tumor diameter was 7 cm ± 5.3 (0.3-25). 50 BBA viewed in median mitotic count was 6.0 ± 14.64 (0-94.0).

C-kit (CD-117) was positive in 104 (93.7%) cases and negative in 7 cases (6.3%). CD 34 was positive in 80 cases (72.1%) and negative in 31 cases (27.9). DOG1 were evaluated in 78 cases as there was 33 insufficient tissue samples. DOG1 was positive in 68 cases (61.3%) while negative in 10 patients (9%). DOG1 was

Table 2. Ki-67 relationship with other parameters

Varýables		KÝ-67 n (%)		*P* value
		Positive	Negative	
c-kit	positive	85 (93.4)	19 (95)	0.631
	negative	6 (6.6)	1 (5)	
CD34	positive	64 (70.3)	16 (8%)	0.282
	negative	27 (29.7)	4 (20)	
SMA	positive	61 (67)	73 (65.8)	0.361
	negative	30 (33)	38 (34.2)	
S-100	positive	65 (71.4)	82 (73.9)	0.167
	negative	26 (28.6)	29 (26.1)	
desmin	positive	14 (15.4)	2 (10)	0.415
	negative	77 (84.6)	18 (90)	
Early stage		71 (78)	18 (90)	0.185
Advanced stage		20 (22)	2 (10)	
Mitosis number	< 5	35 (38.5)	17 (85)	0.001
	5-10	33 (36.3)	2 (10)	
	> 10	23 (25.3)	1 (5)	
Tumor size	< 2 cm	13 (14.3)	2 (10)	0.438
	2-5 cm	18 (19.8)	5 (25)	
	5-10 cm	41 (45.1)	6 (30)	
	> 10 cm	19 (20.9)	7 (35)	
Location	gastric	37 (40.7)	4 (20)	0.067
	Non-gastric	54 (59.3)	16 (80)	
Ýncidentally	yes	8 (8.8)	3 (15)	0.314
	No	93 (91.2)	17 (85)	
Metastasis	yes	14 (15.4)	0 (0)	0.051
	no	77 (84.6)	20 (100)	
Recurrence	yes	11 (12.1)	2 (10)	0.573
	No	80 (87.9)	18 (90)	

with +1 (36.5%) positiveness in 23 cases, +2 in 23 patients (36.5%), +3 in 17 patients (28%). A relation was present between c-kit (CD-117) and DOG1 which diagnosed actually with immunohistochemical method.

(*P* = 0.041) there were 64 (90%) cases with C-kit positive and DOG1 positive; 4 (57.1%) cases with c-kit negative and DOG1 positive. 3 (42.9%) of cases were both negative. the diagnostic specificity of DOG1 was 94.1%, the specificity was 42.9%. When DOG 1 was used with c-kit, in the diagnosis accuracy rate was 85.9%. DOG1 the relationship with other parameters has been found insignificant and they are shown in **Table 1**. ki-67 were positive in 91 (82%) cases and negative in 20 (18%). The average prevalence percentage of Ki-67 was 6.58% ± 9.1. 28 (25.2%) cases staining over 10%, while in 83 cases (74.8%) under the 10n% staining was present. Ki-67 were associated with a significant number of mitosis. (*p* value 0.001). Ki-67 showed a positive correlation with the number of mitosis. Ki-67, the relationship with other parameters has been found insignificant and they are shown in **Table 2**.

Lymph node metastasis was present in 1 patient. 89 (80.2%) patients were early stage, 22 patients (19.8%) had advanced stage. According to the NIH 2002 consensus risk classification of early stage patients, 42 (47.2%) patients at high risk, 13 (14.6%) intermediate-risk group, 21 (23.6%) in low risk group, 13 (14.6%) was in the very low risk group. The median survival time of patients with early-stage was 64 months (2-171 months), whereas; the median survival time of patients with advanced disease was 62 months (5-142 months). 87 (78.4%) patients were alive, 24 (21.6%) patients had been ex during follow-up. Patient demographic data, clinical features, pathological features and immunohistochemical features are summarized in **Table 3**.

Follow-up after surgery in patients with primary tumor size and mitotic count, based on the risk classification, no correlation was found between life expectancy (P = 0.180). In these patients there was no correlation between age, gender, Ki-67, DOG1, tumor location, tumor diameter (*P* values were 0.19, 0.65, 0.704, 0.130, 0.47, 0.076).

Follow-up after surgery in patients with primary mitotic count had a significant correlation between the life time. (*P* = 0.023), number of mitosis less than 5 up to 50 BBA, while median survival time was 142.9 ± 10.6 months; 5-year survival ratio was 97%. Those number of mitosis between 6-10, while median survival time was 132.66 ± 9.84 months, 5-year survival ratio was 83%. Number of mitosis above 6-10, while median survival time was 91.6 ± 15.09 months, 5-year survival ratio was 65%.

There was no significant difference in advanced stage patients between tumor size, tumor enclave, mitotic count, Ki-67, gender and the life time. *p*-values respectively (0.33, 0.50,

Table 3. Distribution of patients

Varables		N (%)
Sex	male	53 (47.7)
	female	58 (42.3)
Location	Gastric	41 (36.9)
	Colon	8 (7.2)
	Small intestine	48 (40.3)
	Omentum	12 (10.8)
	Esophageal	1 (0.9)
	Retroperitoneal	1 (0.9)
Ulcer	yes	85 (76.6)
	no	26 (23.4)
Necrosis	yes	67 (60.4)
	no	44 (39.6)
Bleeding	yes	51 (45.9)
	no	60 (54.1)
Distant metastases	yes	97 (87.4)
	no	14 (12.6)
Lymph node metastasis	yes	110 (99.1)
	no	1 (0.9)
c-kit	Positive	104 (93.7)
	Negative	7 (6.3)
CD34	Positive	80 (72.1)
	Negative	31 (27.9)
SMA	Positive	73 (65.8)
	Negative	38 (34.2)
S-100	Positive	82 (71.9%)
	Negative	29 (29.1%)
KÝ-67	Positive	91 (82.0%)
	Negative	20 (18.0%)
Desmin	Positive	16 (14.4%)
	Negative	95 (85.6%)
Risk group	High risk	42 (47.2%)
	Mid-risk	13 (14.6%)
	Low-risk	34 (38.2%)
Cell type	Spindle	87 (78.4)
	Mixed	16 (14.4)
	Epitheloid	8 (7.2)
Recurrence	Yes	98 (88.3)
	No	13 (11.7)
DOG1	Positive	68 (61.3)
	Negative	10 (9.0)
Stage	Early stage	80 (80.2)
	Advanced stage	22 (19.8)
Tumor size	< 2 cm	15 (13.5)
	2-5 cm	23 (20.7)
	5-10 cm	47 (42.3)
	> 10 cm	26 (23.4)
Staining intensity	+1	23 (36.5)

0.25, 0.31c3, 0.69). Of patients with advanced stage between the ages of 50 to 60 the 5-year survival percentage was 55.6% while it was 37.5% of those over age 60 ($P = 0.036$).

Life expectancy of patients with advanced-stage borderline significance was found between DOG1 positiveness and negativeness ($P = 0.061$). Median survival time of DOG1 positive patients was 142 months, while 15 months in DOG1 negative patients.

No significant relationship was found between age, sex, tumor location, tumor size, Ki-67, DOG1 and the recurrence. (p values 0.26, 0.356 respectively, 0.67, 0.58, 0.47, 0.74) there was no significant correlation between recurrence and risk groups (p = 0.026) after primary surgery in high-risk groups, the patients followed up for 5 years and recurrence rate was 21%; no recurrence was observed in very low and low risk patients.

Mitosis has a significant correlation with the number of relapses (P = 0.032) Mitotic count of less than 5 in 50 BBA recurrence rate was 16% in 5 years, with 5-10 mitotic count range was 23%, with those over 10 range was 32%.

Discussion

Gastrointestinal stromal tumors are all of the most common mesenchymal tumors of the digestive system [1, 2]. Gender does not constitute a significant risk factor for the disease. In our study and in several studies reported that no significant difference in gender distribution between patients. at the same time a significant relationship was not found between sex and recurrence and survival. Generally, the 5th and 6th decade is the most commonly diagnosed age group of patients [11, 12]. In parallel to the literature, the median age in our study group was found to be 58. In our study, a significant relationship was not detected between age and recurrence; but it is observed that survival decreases as age progression in patients with advanced stage. The reason for this is due to age-

	+2	23 (36.5)
	+3	17 (27.0)
Staining ratio	< 50	3 (4.8)
	50	9 (14.3)
	60	5 (7.9)
	70	7 (11.1)
	80	11 (17.5)
	90	8 (12.7)
	100	20 (31.7)
Distant metastases	yes	14 (12.6)
	No	97 (87.4)
Metastatic location	hepatic	11 (78.6)
	extrahepatic	3 (21.4)
Mitosis number	< 5	52 (46.8)
	5-10	31.5 (78.4)
	> 10	24 (21.6)
Incidentally		11 (8)
		Mean ± ss Median (min-max)
Age		55.61 ± 13.33 58.0 ± (11.0-83.0)
Mitosis		9.84 ± 14.64 6.0 (0.0-94.0)
Ki-67		6.58 ± 9.10 4.0 (0.0-60.0)
Tumor size		7.83 ± 9.30 7.0 (0.3-25.0)

related comorbid condition or already to be at an advanced stage.

GIST, are usually asymptomatic and often detected incidentally. In symptomatic patients, the most common complaints are vague abdominal pain as stated. These findings most of the time may accompany with non-specific gastrointestinal symptoms such as early satiety, bloating, constipation, nausea, vomiting. However, in patients with late diagnosis intestinal obstruction, perforation, obstructive jaundice, bleeding is seen and can lead to serious gastrointestinal complications with high morbidity and mortality [13]. In our study, three patients were operated because of ileus and than diagnosed as GIST. Therefore, although the variability of clinical findings does not help clinicians in diagnosis, particularly GIST should be kept in mind in elderly patients with subclinical gastrointestinal complaints. GIST are 20% asymptomatic and 10% of cases are detected during the autopsy [13]. However, in our study, 11 (9%) cases were found incidentally. 2 of them were in the high risk group, 2 in the intermediate-risk group, 4 in the low-risk group, while the third was with a very low risk group. All of the cases whom detected incidentally was in early stage.

Although it may appear all along the digestive tract, GIST are most often shows placement in the stomach (50-60%). Small bowel (25-30%), colon-rectum (5-15%), esophagus (2%) are other enclaves [13-16]. Although in our study the number of patients with GIST localized in the small intestine were more of others, this can be due to our work done by considering a certain time interval.

Several studies have found a significant correlation between clinical results and localization [15, 17]. Emory and friends reported that of survival in small bowel tumors at worst, it is the best in esophageal tumors. In the same play it is shown that tumor localization is an independent prognostic marker from age, tumor size and mitotic rate [15]. Nakamura et al in their study with 80 cases they reported that there was no significant difference at survival in two series, one with tumors localized in the stomach the other tumors not localized in the stomach [18].

No significant correlation was found between the recurrence and Tumor residential area. Often the cause of differences in prognosis by placement of the tumor is considered to be caused by the presence of the different mutations.

Surgery is the treatment of GIST. In patients with large tumors, neoadjuvant imatinib therapy may be given, after than surgery can be administered. Unresectable, recurrent or metastatic, medium and high-risk patients, a tyrosine kinase inhibitor imatinib mesylate, was recommended to use. Many studies conducted 55% remission and progression stops at 70-80% of patients [8]. Sunitinib treatment can be given to patients with resistance to imatinib therapy. In our study, the number of patients receiving imatinib therapy was 77 (69.4%). 22 of the treated patients were in advanced stage and 55 of these patients in the early stage and were all at middle and high-risk groups. Three patients were switched to sunitib treatment from imatinib. Immunohistochemical staining

are used in the differential diagnosis of mesenchymal tumors. Most of mesenchymal tumors are positively stained with the c-kit (CD-117) [14, 19]. Hirota et al reported c-kit expression in 94% of GIST cases [1].

Another consideration to keep in mind is that 5% of GIST can be painted negatively with c-kit. Due to this new immunohistochemical markers are under investigation as an alternative to expensive mutation analysis. Recently, one of which was focused on the most important marker is DOG1. In the study of Espinosa et al in 425 cases they showed that DOG1 has a high specificity and sensitivity in the diagnosis of GIST and DOG1 positivity was 87% and 74% positiveness for c-kit [4]. West et al, they studied on 149 cases and showed that DOG1 positivity was 97.8%, the c-kit positivity was 94% in GIST [5] in the study of Miettinen et al at 1168 GIST cases DOG1 positivity was 94.8%, the c-kit positivity was 94.9%. Also in this study, c-kit were thought to be more sensitive in small bowel tumors [20]. In our study, only 78 patients were evaluated over DOG1 positivity due to inadequate tissue and stands out as a marker supporting the diagnosis. DOG positivity were found as 87% and c-kit as 93.7%.

In our study, the specificity and sensitivity of DOG1 respectively, were found to be 94.1% and 42.9%. Although DOG1 is used as a marker for differential diagnosis in many studies, it is interesting that there is not sufficient data of these markers in the literature about the impact on prognosis and survival. According to our investigations of seventy-eight patients, any effect was not observed on survival and the prognosis of patients with follow-up after primary surgery. However, DOG1 considering the relationship with other parameters, although not statistically significant in GIST patients at advanced stage we've found that DOG1 (-) negativeness might indicate to poor prognosis and may suggest other sarcomas in the diagnosis. This data by increasing the sample size is needed to be supported by studies. Also no relation was found between DOG1 with recurrence and tumor location.

Other immunohistochemical staining that are used in the evaluation of GIST are SMA, desmin, S-100 and CD-34. similar to our work due to various studies CD-34 in GIST was with 72-78% positive staining [2, 21]. SMA was 19-57% positive in GIST [22-25].

SMA positivity rate of 72.1% in our study and this is thought to be related to the large number of small bowel tumors. There was 4.1-5% positiveness of demsin in GIST patients. In our study, 14.4% were positive. S-100 were positive in 6-28% of GIST cases [26, 27]. S-100 was found to be 73.9% positive in our study.

The most common histological type of GIST in our study was spindle cell type [1, 28-30]. However, a significant correlation was not found between histological subtype and prognosis. To determine the clinical behavior of GIST is difficult. 70% benign, 30% may show malignant behavior. The most important factor determining the malignant potential of the tumors are histopathological findings. These are tumor size, mitotic rate, tumor localization, growth pattern, proliferation markers, hemorrhage, necrosis and cellularity. They are also considered as factors affecting prognosis. Tumor size > 5 cm and mitotic rate > 10 in BBA is considered to be poor prognostic factors.

Miettinen et al in their study in 1765 cases of GIST at gastric localization, they reported interestingly that tumors 10 cm above and whom with low mitotic activity have relatively good prognosis and after 5-15 year follow-up metastases developes in 12% of them and therefore tumors should not be automatically reported as malignant due to larger tumor size [31] in our study, no significant relationship was detected between tumor diameter and recurrence or metastasis; but mitotic count above 10 in 50 BBA was found to be significant with recurrence and metastasis.

The most common site of metastases of GIST is the liver, as in our cases (78.6%) [32-34] a significant relationship was not detected between the diameter of the tumor and distant metastasis, but there was a meaningful relationship between mitosis number. ($p = 0.025$) ki-67 index is now known to be a reliable, simple and reproducible method in obtaining information about the tumor proliferative capacity. Increased expression of Ki-67 is associated with the malignant behavior of tumors [6, 18, 35, 36]. Some authors specify that Ki-67 and mitotic rate can be used as a prognostic factor in gastric located GIST, although in our study we found no significant relationship between ki-67 and tumor location. In studies of Ki-67 index it was associated with shorter survival [37]. The publications are also available sug-

gesting that when Ki-67 index is high it indicates as a prognostic factor showing metastasis and recurrence [37-39].

As a result: in this study in predicting the malignant potential effectiveness of ki-67 was assessed. In none of the histopathologically at very low-risk group of patients Ki-67 index was above 10% and no significant correlation was found between ki-67 and survival in early and advanced stage patients. There was correlation between ki-67 and mitotic activity index. Correlation between Ki-67 and mitotic count is an expected status, it should be examined in larger groups of patients that Ki-67 can be used instead of mitotic index.

Disclosure of conflict of interest

None.

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