

# Histopathological and Immunohistochemical Characteristics of Gastrointestinal Stromal Tumors and Risk Group Analysis

## *Gastrointestinal Stromal Tümörlerin Histopatolojik, İmmünohistokimyasal Özellikleri ve Risk Grup Analizi*

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### Öz

**Amaç:** Gastrointestinal stromal tümörler (GİST); gastrointestinal traktın en sık görülen mezenkimal tümörleridir. Gastrointestinal sistemin peristaltizmini düzenleyen interstisyel Cajal hücrelerinden köken aldıkları düşünülmektedir. Gastrointestinal stromal tümörler farklı morfolojik ve biyolojik davranış özellikleri ile heterojen bir tümör grubudur bu nedenle farklı ülkelerde farklı epidemiyolojik, klinikopatolojik ve prognostik özellikler sergileyebilmektedir. Bu çalışmanın amacı, son 10 yılda GİST tanısı alan 100 olgunun histopatolojik, immünohistokimyasal özellikleri ve risk gruplarının analizini yapmaktır.

**Hastalar ve Yöntem:** 2006- 2016 yılları arasında patoloji laboratuvarımızda GİST tanısı alan 100 olgu retrospektif olarak incelendi. Olguların çap ve mitoz oranlarına göre risk grupları belirlendi. Çap ve mitoz dışındaki histopatolojik ve immünohistokimyasal özellikleri ile risk grupları arasındaki ilişki analiz edildi. Verilerin analizinde Chi- kare- Fischer testleri kullanıldı.

**Bulgular:** Olgularımızda yaş ve cinsiyet dağılımı risk gruplarına göre değişmemektedir. En çok; sırası ile kolorektal, ekstra gastrointestinal sistem (mezental, omental ve retroperiton), ince barsak ve mide GİST leri yüksek risk grubunda yer almaktadır. İnce barsak, kolorektal ve ekstra gastrointestinal tümörler daha büyük çaplı olup mide tümörleri daha küçük çaplıdır. İmmünohistokimyasal CD-34, S-100, SMA, desmin ekspresyonu ile risk grupları ilişkili değildir. Ki-67 %10' un üzerinde ekspresyon gösteren tümörler yüksek risk grubunda yer almaktadırlar. Mide ve ekstra gastrointestinal tümörler daha fazla CD-34 ekspresyonu göstermektedir. Nekroz ve kanama gösteren tümörler ile selüleritesi yüksek tümörlerin bir üst risk grubunda olma oddsları artmıştır. Ülserasyon, büyüme paterni ve atipi ile risk grupları arasında ilişki mevcut değildir.

**Sonuç:** GİST ler gastrointestinal sistemin nadir tümörlerinden olup farklı bölgelerde, farklı varyasyonlarda ortaya çıkabilirler. GİST lerin histopatolojik ve immünohistokimyasal olarak detaylı incelenmesi ve risk gruplarına göre klasifiye edilmesi klinik tedavi ve takipte önemli rol oynamaktadır.

**Anahtar Kelimeler:** Gastrointestinal stromal tümör, histopatoloji, immünohistokimya, risk grup

### Abstract

**Aim:** Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal tumours of the gastrointestinal tract. GISTs are thought to originate from the precursors of interstitial Cajal cells which regulate gastrointestinal peristalsis. GISTs include a group of heterogeneous tumors with different morphology and biologic behavior so their epidemiology, clinico-pathological features and prognosis is distinct in different countries. The aim of this study is to analyze the histopathological, immunohistochemical characteristics and risk groups of 100 patients with GIST in the last 10 years in our department.

**Patients and Methods:** Between 2006-2016, 100 patients with GIST diagnosed in our Pathology laboratory were examined retrospectively. Risk groups were determined according to diameter and mitotic rates of the cases. Histopathologic and immunohistochemical features excluding diameter and mitosis were analyzed and the relationship between risk groups was analyzed. A Chi-care- Fischer was used for descriptive statistical analysis.

**Results:** In our cases, there is no relationship between age, gender and risk groups. Colorectal, extra gastrointestinal system (peritoneum, mesentery and retroperitoneum), small intestine and stomach GISTs are in high risk group respectively. Small intestine, colorectal and extra gastrointestinal system tumors are larger diameter than stomach tumors. There is no relationship between immunohistochemical CD-34, S-100, SMA, desmin and risk groups. Tumors expressing over 10% of Ki-67 are in high-risk group. Stomach and extra gastrointestinal tumors represent more CD-34 expression. Tumors with necrosis, haemorrhage and high cellularity are at higher risk group. There is no relationship between risk groups and ulceration, growth pattern and atypia.

**Conclusions:** GISTs are rare tumors of the gastrointestinal tract and may occur in different regions, in different variations. Detailed histopathologic and immunohistochemical examination of the GISTs and classification according to risk group plays an important role in clinical treatment and follow-up.

**Keywords:** Gastrointestinal stromal tumours, histopathology, immunohistochemistry, risk group

## INTRODUCTION

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of the gastrointestinal

tract (1). GISTs develop from the interstitial cells of Cajal (2). It is estimated that GISTs affect about 10-20 million people annually in the whole world (3).

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There are findings that some series of GISTs are seen more in males and some have reported that the prevalence of males and females is equal (4). The most common localization is stomach, followed by small intestine, colon, rectum and abdominal cavity. Clinical presentation is very varied and depends on tumor size and localization. GISTs demonstrate 3 cell types as spindle, epithelioid and mixed (spindle and epithelioid) type (5). Estimated 85% of GIST tumors were found to have an active mutation in the kit proto-oncogene while only 3–5% mutation in PDGFRA (6). Primary treatment for localized tumors is surgical resection. For advanced stage metastatic tumors, surgical treatment can be performed after neoadjuvant therapy (7).

GISTs are clinically and morphologically variable and may behave in a wide range from benign to malignant. For this reason, it is difficult to predict the biological behavior of the tumor. The most important and easily applicable histological criteria are tumor size (maximum diameter) and mitosis (8-11). Studies have shown that  $\leq 5$  mitoses are interpreted in favor of benign behavior, especially in stomach GISTs at 50 high power fields (HPF) (8). Tumors showing  $> 5$  mitosis in 50 HPF have the high risk for intraabdominal and hepatic metastasis (12). Tumors 2 cm or less in diameter are also thought to exhibit benign behavior. The use of tumor cellularity and atypia is recommended, but practicability remains a problem (8).

In this study, risk groups were determined according to diameter and mitosis rates of GIST diagnosed cases in our laboratory, the relationship between risk groups and other histopathologic and immunohistochemical features except mitosis and diameter were analyzed.

## PATIENTS AND METHODS

Between 2006 and 2016, 100 patients with GIST diagnosed in our pathology laboratory were retrospectively studied. Surgical resection materials of patients who had not previously received neoadjuvant treatment were included in the study and needle biopsies or cytological materials were excluded from the study. In the cases, distribution according to age, sex, localization, tumor diameter, mitotic activity counts in 50 HPF, cell type, growth pattern, atypia, cellularity, necrosis, hemorrhage and ulceration were evaluated. In addition, the immunohistochemical analysis was performed. CD-117, CD-34,  $\alpha$ -Smooth Actin (SMA), desmin, S-100 and proliferation indices of Ki-67

**Table 1.** Fletcher's risk classification.

Risk group	Tumor Diameter	Mitosis
Verylow	<2 cm	<5
Low	2-5 cm	<5
Intermedier	<5 cm	6-10
	5-10 cm	<5
High	>5 cm	>5
	>10 cm	Anymitosis
	Anydiameter	>10

immunohistochemical staining were evaluated. The cases were classified according to the risk groups as very low, low, intermedier and high according to tumor diameter and mitotic count (Table-1) (13). The relationship between risk groups and other histopathologic findings and immunohistochemical data except mitosis and diameter were analyzed.

Continuous variables are given as mean $\pm$ std or median (min-max). Categorical variables are given as frequencies and percentages. Fisher and Chi square tests are applied to investigate relationships between categorical variables. A backward ordinal logistic regression model is formed to find out relevant variables with risk group. SAS University Edition 9.4 was used. A p value  $<0.05$  is considered significant.

## RESULTS

In the cases the average age is  $59.95\pm 13.76$  and the female to male ratio is equal. 50% of the cases are localized in stomach, 23% are small bowel, 17% are extra gastrointestinal system (extra GIS; peritoneum, mesenteric and retroperitoneal) and 10% are large intestine. The medyan tumor diameter is 6 cm (0,4-35). (14% cases  $\leq 2$  cm, 22% cases  $>2- \leq 5$  cm, 40% cases 5-10 cm, and 24% cases 10 cm). The medyan mitosis is 4 (0-220) dür. ( $\leq 5/10$  HPF (66 cases), 6-10/10 HPF (12 cases),  $>10/10$  HPF (22 cases)) (Table 2). Cell type is 60% spindle, 12% epithelioid and 28% mix. The cases have a mild atypia at 72% and a severe atypia at 28%. The growth pattern is expansive in 77% and infiltrative in 23% of cases. 87% of the tumors are cellular and 23% are less cellular. The cases had necrosis in 27%, haemorrhagia in 48% and mucosal

**Table 2.** Age, diameter and mitosis analysis in cases.

Variable	Mean	Median	Std Dev	Lower Quartile	Upper Quartile
Age	59.95	61.00	13.76	50.50	70.50
Diameter	7.57	6.00	5.59	3.75	9.50
Mitosis	9.90	4.00	24.14	2.00	7.50

**Table 3.** Localization and risk groups analysis

Localization	RiskGroups n(%)			Total
	Very low/ low	Intermedier	High	
Stomach	23(46)	16 (32.0)	11 (22)	50
Small Bowel	7 (30.4)	4 (17.4)	12 (52.1)	23
Large Bowel	1(10.0)	1 (10.0)	8 (80.0)	10
Mesentery/omentum	3 (17.65)	2 (11.76)	12 (70.59)	17
Total	34	23	43	100

ulceration in 19%. Immunohistochemically CD-34 is 75% positive, SMA (smooth muscle actin) is 31%, desmin is 12% and S-100 is 23%. All of the cases are positive with CD-117. The Ki-67 proliferation index is  $\leq 10\%$  at 66% and  $>10\%$  at 34% of the cases. 11% of the cases are very low, 23% are low, 23% are intermedier and 43% are in high risk group.

In the risk group analysis according to age, although younger age groups are more likely to be at high risk groups, they are not statistically significant. While the rate of very low and low risk groups is 42% at ages 60 over, the rate of intermedier and high risk groups is 50% at ages 60 and below.

Gender distribution does not depend on risk groups. When localization and risk groups are evaluated, the most common tumors are colorectal, extra GIS, small intestine and stomach localized tumors, respectively in the high-risk group (p: 0.008) (Table 3).

While cell type distribution does not differ in risk groups, the group with the mix-cell type was in the higher-risk group, the epithelioid group is in the mostly low-risk group. There is no significance in the spindle group. Stomach, colorectal and extra GIS localized tumors are mostly spindle and small intestine tumors show more mixed morphology but not statistically significant.

Localization and tumor diameter are related. Colorectal, small intestine and extra GIS located tumors are larger in diameter, stomach-located

tumors are less in diameter (p: 0.041) (Table 4).

There is significance only in Ki-67 between immunohistochemical staining and risk groups. 10% or less expression of Ki-67 are found in the very low and low risk groups and over 10% of expression are found in the high risk group (p<0.0001) (Table 5). CD-34 and Ki-67 are significant among immunohistochemical stainings according to localization. Stomach and extra GIS derived tumors express more CD-34 (p: 0.0002). Most colorectal and extra GIS located tumors express Ki-67 more than 10%, whereas the stomach and small intestine localized tumors express 10% or less (p <0.0001). Although there is no significant difference statistically in SMA staining, small intestine-localized tumors show more positive expression (Table 6).

Tumors that have necrosis and hemorrhage and more cellular tumors have increased the odds of being in an upper risk group (Table 7).

There was no relationship between the risk groups and the mucosal ulceration, atypia and growth pattern.

## DISCUSSION

GISTs are a heterogeneous group of tumors with different morphological features and biological behavior. For this reason, epidemiology, clinical course and treatment response may vary in different regions (14). GISTs are seen most frequently between the ages of 55 and 65 over the age of 40 (2). In our study, the average age of our patient population was 59.95 and

**Table 4.** The analysis of tumor localization and diameter

Localization	Diameter (cm)				Total
	$\leq 2$	2-5	5 -10	$>10$	
Stomach	11	13	21	5	50
	22.00	26.00	42.00	10.00	
Small Bowel	2	6	7	8	23
	8.70	26.09	30.43	34.78	
Large Bowel	0	2	4	4	10
	0.00	20.00	40.00	40.00	
Mesentery/Omentum	1	1	8	7	17
	5.88	5.88	47.06	41.18	
Total	14	22	40	24	100

**Table 5.** Immunohistochemistry-risk group analysis

IHC	Risk Groups n (%)		
	Very low/low	Intermedier	High
CD-34 (+)	28 (37.33)	18 (24.0)	29 (38.67)
SMA (+)	11 (35.48)	8 (25.81)	12 (38.71)
Desmin (+)	4 (33.35)	4 (33.35)	4 (33.3)
S-100 (+)	8 (34.78)	7 (30.44)	8 (34.78)
Ki-67(over %10)	3 (8.82)	3 (8.82)	28 (82.36)

found to be in accordance with the literature. Although there was no statistically significant difference in risk group analysis according to age, it was found that 60 and under age group were in higher risk groups than over 60. There are studies in the literature that have different results on the effect of age on prognosis. In a study of GISTs seen in the Chinese population, it was reported that patients over 60 years of age had a longer survival time (14). However, another study has showed that tumors seen in younger age have better prognosis (15).

There are findings in some series of GISTs that they are seen more in mens and it is said that the prevalence of men and women is equal in some series (4). In our cases, the rates of men and women were found to be equal. There was no difference in gender and risk group analysis. Although there are articles in which GISTs show better prognosis in women (15), there are also articles that show that there is no difference between genders as in our study (14).

GISTs have localized most frequently in stomach (60-70%), small intestine (25-35%), colorectal (5%) and esophagus (<2%) (16). They may also be found in the omentum and the mesentery as primer (16). Peritoneum, mesenteric and retroperitoneal GISTs were grouped as extra GIS in our study. Our cases are located in stomach (50%), small intestine (23%), extra GIS (17%) and colorectal location (10%). The most common location of the stomach and small intestine is consistent with the literature, but colorectal and especially extra GIS cases are higher the mentioned ones. This suggests that some of the extra GIS located tumors that come to our clinic may

be a metastatic lesion whose primary is unknown. Esophageal GISTs is not available in our series. This suggests that epidemiologically, GISTs may vary in the frequency of localization in different regions. In the analysis of localization and risk groups, stomach tumors are located in the lowest risk group then the small intestine, extra GIS and colorectal tumors are listed respectively. Findings are consistent with published reports that gastric tumors exhibit less aggressive behavior (14,17).

Two of the most important independent parameters for determining risk groups in GIST are tumor diameter and mitosis. Because the tumor diameter is  $\leq 2$  cm and  $\leq 5$  mitosis at 50 HPF, the tumor is interpreted in favor of showing benign behavior (4, 13). We determined the risk groups according to the diameter and mitotic index of our cases. We also reached the conclusion that the tumor diameters differ according to the localizations. We have found that the stomach tumors are smaller in diameter. In the literature, it has been reported that stomach and rectal tumors are smaller, small intestine and colon tumors are larger in size. This finding suggests that the diameter alone may be a significant prognostic indicator and that gastric tumors show less aggressive behavior than other localizations.

Although there is no statistically significant difference between cell type and risk group. But epithelioid cell type tumors are mostly in the low risk group and mixed cell types are mostly in the high risk group in our study. Stomach, colon and extra GIS located tumors are mostly spindle, small intestine tumors show more mixed cell morphology.

**Table 6.** Localization-immunohistochemistry analysis

Localization	Immunohistochemistry				
	CD-34(+)	SMA(+)	Desmin(+)	S-100 (+)	Ki-67 (over%10)
Stomach	46 (92.0)	15 (30.0)	7 (14.0)	9 (18.0)	8 (16.0)
Small Bowel	12 (52.17)	11 (47.83)	3 (13.04)	7 (30.43)	7 (30.43)
Large Bowel	5 (50.0)	1 (10.0)	0 (0.0)	1 (10.0)	8 (80.0)
Mesentery/omentum	12 (70.59)	4 (23.53)	2 (1.76)	6 (35.29)	11 (64.71)

**Table 7.** Odds ratio estimates of cellularity, necrosis and hemorrhage

Effect	Point Estimate	Odds Ratio Estimates		Pr > ChiSq
		95% Wald	Confidence Limits	
<b>Cellularity</b> high / low	4.678	1.373	15.938	0.0136
<b>Necrosis</b> positive/negative	4.370	1.283	14.881	0.0183
<b>Hemorrhage</b> positive/negative	3.406	1.328	8.738	0.0108

Although there are articles in the literature that tumors in the epithelioid cell type are associated with poor prognosis (18,19), there are also articles that higher survival rates of tumors in epithelioid cell type (14). It is currently not possible to use the cell type as an independent parameter.

All of our cases were CD-117 positive, 75% CD-34, 31% SMA, 23% S-100 and 12% desmin positive. A limited number of studies are available on the association between immunohistochemical studies and risk groups. Liang et al. have reported that CD-34 tumors are more aggressive (20). Chiriac et al. have reported that CD-34, SMA, S-100 and desmin expression is not related to surveillance (21). According to Miettinen et al., GISTs are positive at the ratio of 70-80% with CD-34 and most common in stomach and small intestine tumors. Esophagus and rectal tumors indicate more CD-34 negative. SMA is positive at the 30% ratio, most commonly in stomach and small intestine tumors, S-100 is positive at 10% ratio and commonly in small intestine tumors. Desmin is positive at 2-4% ratio and most commonly in esophageal GISTs (4). In our cases, CD-34 and SMA positivity is in accordance with the literature and we have high S-100 and desmin staining rates. Stomach and extra GIS located tumors are more CD-34 positive in our series. This finding may be due to greater of our extra GIS located tumor count compared to the series in the literature. Further studies involving more extra GIS located tumors may be needed. SMA positivity was detected most commonly in small intestine tumors. We could not comment on esophageal tumors because we did not have esophageal tumor in our series.

Tumors with an immunohistochemical Ki-67 ratio of 10% or less are located in the very low and low risk group, and the cases showing the over 10% expression are located in the high risk group. In addition, tumors of the stomach and small intestine showed lower Ki-67 expression. In the literature, cases showing Ki-67 positivity above 10% were reported to be associated with metastasis and tumor-associated deaths. In our series, the stomach and then small intestine tumors

are located in the low-risk group, this is also consistent with our Ki-67 ratios. It is stimulating that Ki-67 rates should be included in pathology reports.

In our study, the rates of being in an upper-risk group of tumors with necrosis and haemorrhagia and tumors with high cellularity were found to be high. However, no correlation was found between risk groups and mucosal ulceration, atypia, and tumor growth pattern. There are articles in the mentioned histopathological features literature that invasive growth pattern, necrosis and mucosal ulceration are associated with poor prognosis (22). In a study that classified GISTs as benign and malignant according to mitosis and diameter and that clearly defined the tumors that could not enter the benign and malign categorization as borderline, borderline tumors showing invasive growth pattern, necrosis and cytologic atypia were the aggressive course (23).

In summary; we classified our cases according to their diameter and mitotic rates. We assessed whether there was any association between risk groups and features such as age, sex, tumor location, cell type, cell atypia, cellularity, growth pattern, necrosis, hemorrhage, mucosal ulceration and immunohistochemical findings. In conclusion, GISTs are a heterogeneous group of tumors with different morphological features and biological behaviors and may differ in terms of histopathological and immunohistochemical characteristics affecting the epidemiological and risk group. More studies involving more cases in different regions will be needed. Histopathologic features and immunohistochemical findings other than diameter and mitosis should be included in the pathology reports in order to guide the clinician and to provide a prognosis in the risk classification.

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