

Prognostic Value of Her2/neu Expression in Gastrointestinal Stromal Tumors: Immunohistochemical Study

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Ahmed M Abd El-Aziz¹, Eman A Ibrahim², Ashraf Abd-Elmoghny¹, Mohammed El-Bassiouny³, Zina M Laban⁴, Somaia A Saad El-Din² and Youhanna Shohdy¹

¹Department of General Surgery, Faculty of Medicine, Ain Shams University, Cairo, Egypt. ²Department of Pathology, Faculty of Medicine, Ain Shams University, Cairo, Egypt. ³Department of Oncology, Faculty of Medicine, Ain Shams University, Cairo, Egypt. ⁴Columbia University, NY, USA.

ABSTRACT

BACKGROUND: Gastrointestinal stromal tumor (GIST) is a relatively rare type of neoplasms. In Egypt, it represents 2.5% of gastrointestinal tumors and 0.3% of all malignancies. Most of the GISTs develop in the stomach.

AIM: To reveal the significance of Her2/neu immunohistochemical expression in GIST and its correlation with other histopathologic parameters and tumor relapse after regular follow-up.

PATIENTS AND METHODS: This study is a retrospective and prospective cohort. It included 32 patients with GISTs, who were resectable with no distant metastasis. Immunohistochemical staining by Her2/neu was performed after complete surgical resection of the tumors with preservation of the pseudocapsule.

RESULTS: In total, 53.1% of cases were men and 46.9% women. Tumors were classified into low-risk (25%), intermediate-risk (21.9%), and high-risk groups (53.1%). Her2/neu expression was negative in 56.3% of GISTs and positive in 43.7%. Its expression was significantly correlated with risk grade ($P = .04$), tumor size ($P = .001$), mitotic count ($P = .00$), and increased risk of relapse ($P = .00$). Furthermore, tumor relapse was significantly correlated with the tumor mitotic counts ($P = .00$). Using kappa agreement test, it showed that 4 mitotic counts/50 high-power fields (HPF) was the cutoff value with which the tumor might be associated more with relapse, with 83% sensitivity, 70% specificity, and P value of .003.

CONCLUSIONS: Her2/neu might be used as an independent prognostic marker for tumor recurrence after complete resection of GIST, and the cutoff value of mitotic count that might predict tumor relapse is 4/50 HPF. However, more clinical studies with greater number of cases with fluorescent in situ hybridization integration are recommended.

KEYWORDS: gastrointestinal stromal tumors, Her2/neu, immunohistochemistry, relapse, mitotic count

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CORRESPONDING AUTHOR: Eman A Ibrahim, Department of Pathology, Faculty of Medicine, Ain Shams University, Alabassiya Square, Zip Code: 11841, Cairo, Egypt. Email: emanpathology@yahoo.com

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common primary mesenchymal neoplasms of the gastrointestinal tract (GIT). In Egypt, it represents 2.5% of gastrointestinal tumors and 0.3% of all malignancies.^{1,2} About 30% to 50% of GISTs have malignant behavior, and metastases are observed in 50% despite initial surgical resection. The most common site of GIST is the stomach (50%–60%) followed by the small intestine (20%–30%); about 10% of GISTs arise from the colon and rectum, and less than 5% are located in the esophagus.³

Gastrointestinal stromal tumors are derived from the interstitial cells of Cajal (ICCs) which are innervated cells associated with the Auerbach plexus that has autonomous pacemaker function and coordinates peristalsis throughout the GIT. The ICC is a myoid cell of mesenchymal origin, and it has some features in common with neural crest-derived cells.⁴

Gastrointestinal stromal tumors carry a mutation in the *kit* gene located on chromosome 4 that encodes a transmembrane

protein (CD117) with intrinsic tyrosine kinase activity that serves as a receptor for the growth factor (stem cell factor), which once activated propagates a cascade of activities leading to cell division. The mutation in the *kit* gene causes uncontrolled activation of the tyrosine kinase independently of the growth factor with uncontrolled cell proliferation. Multiple downstream signaling pathways can thus be activated. The identification of CD117 is a key marker for the diagnosis of GIST in 95% of patients.^{5,6}

Her2/neu (the human epidermal growth factor receptor 2) gene is localized to chromosome 17q and encodes 185-kDa transmembrane glycoprotein with intrinsic tyrosine kinase activity which is involved in signal transduction of many pathways that ultimately affect cell proliferation, survival, motility, and adhesion.⁷ Her2/neu marker has been shown a prognostic significance in many human malignancies, such as breast cancers,^{8,9} some tumors with neuroblastic differentiation,¹⁰ and



gastric adenocarcinoma.¹¹ Thus, it seems that both Her2/neu and CD117 shared many of their signaling pathways; crosstalk between both signaling pathways may also be suspected, but whether overexpression of Her2/neu that may be incorporated in GIST and the mutation of CD117 work independently or potentiate each other needs more studies.¹²

The biological behavior of GIST can be highly variable. Prediction of prognosis of GIST has been studied thoroughly; tumor size and mitotic activity were 2 crucial factors in the risk classification system originally proposed by Fletcher and colleagues.¹³

The aim of this study is to reveal the significance of Her2/neu immunohistochemical expression in GIST and its correlation with other histopathologic parameters and tumor relapse after regular follow-up.

Patients and Methods

Patients and data collection

This is a retrospective and prospective cohort study, the protocol of which was approved by the Hospitals' Ethical Committee (IRB0006379, November 9, 2013). It was conducted between January 2010 to December 2014 in El-Demerdash and Ain Shams University Specialized hospitals (ASUSH). All patients gave their informed consents before enrollment.

We recruited patients with GISTs; some were from archival files of the surgery department and the computer database of the pathology laboratories, and others were newly diagnosed GISTs. The inclusion criteria were that the tumor should be surgically resectable and immunohistochemically positive to CD117. Exclusion criteria were as follows: (1) extra GIT GISTs, (2) metastatic GISTs, and (3) patients received a preoperative neoadjuvant imatinib.

Surgery and follow-up

Surgical local resection was performed after preoperative laboratory and radiological investigations. The excision was done with preservation of the pseudocapsule. Postoperative follow-up for recurrence by pelvi-abdominal computed tomography (CT) was performed for the patients every 3 months twice, then every 6 months 3 times, with a total follow-up period of 2 years. Criteria for recurrence included the development of new lesions that could be detected by CT scan, 2 to 3 cm in size, at the site of the previous tumor and/or the development of metastasis (in liver or peritoneum).¹²

Histopathologic examination

Histopathologic workup was done through the hematoxylin-eosin and CD117 that revealed cytoplasmic staining with cell membrane accentuation. Mitosis was counted manually in 50 high-power fields (HPF).

The patients were divided into 3 categories (high risk, intermediate risk, and low risk) according to the size of the tumor and number of mitosis/50 HPF:¹³

- Very low risk: tumor size <2 cm; mitotic figures <5/50 HPF.
- Low risk: tumor size 2 to 5 cm; mitotic figures <5/50 HPF.
- Intermediate risk tumor size <5 cm; mitotic figures 5-10/50 HPF or 5 to 10 cm; <5/50 HPF.
- High risk: tumor size >5 cm; mitotic figures >5/50 HPF or tumor size >10 cm; any mitosis or any size; >10/50 HPF.

Immunohistochemical analysis

Paraffin-embedded tissue sections were immune-stained for Her2/neu using HercepTest (Rabbit Anti-Human Her2 Protein, Code K5204; Dako Denmark A/S, Glostrup, Denmark). The staining was performed in ASUSH histopathology laboratory using automated immunostainer (BenchMark GX; Ventana Medical Systems, Inc. Basel, Switzerland) according to the manufacturer's instructions.

Two experienced pathologists who were unaware of the risk group the tumor belonged to examined the stained slides independently, and any differences between the 2 pathologists were discussed, with agreement about the final diagnosis. The evaluation of Her2/neu-stained slides was done as follows¹¹:

- 0: no reactivity or membranous reactivity in <10% of tumor cells.
- 1+: faint/barely perceptible membranous reactivity in \geq 10% of tumor cells; cells are reactive only in part of their membrane.
- -2+: Weak to moderate complete, basolateral, or lateral membranous reactivity in \geq 10% of tumor cells.
- 3+: strong complete, basolateral, or lateral membranous reactivity in \geq 10% of tumor cells.

Statistical analysis

Data were then imported into Statistical Package of the Social Sciences (SPSS version 20.0) software for analysis. Qualitative data were represented in number and percentage, whereas quantitative data group was expressed in mean \pm standard deviation.

Differences between frequencies (qualitative variables) and percentages in groups were compared by chi-square test. Differences between parametric quantitative independent groups were calculated by test nonparametric by Mann-Whitney \times analysis of variance nonparametric by Kruskal-Wallis.

Receiver operating characteristic curve (kappa agreement test) was used to calculate the cutoff value of Her2/neu immunohistochemical staining score. *P* value was set at <.05 for significant and <.001 for highly significant results.

Results

We could recruit 39 cases of GISTs; 20 cases were recently diagnosed, whereas 19 cases were retrieved from the archival files. One tumor was negative to CD117, and 6 cases lost the follow-up schedule due to various reasons, such as death in 2 patients

Table 1. Frequency distribution for the demographic and clinicopathologic data of the patients.

		FREQUENCY	PERCENTAGE
Sex	Male	17	53.1
	Female	15	46.9
Site	Stomach	10	31.3
	Ilium	7	21.9
	Duodenum	5	15.6
	Jejunum	5	15.6
	Colon	3	9.4
	Cecum	1	3.1
	Rectum	1	3.1
Risk	High	17	53
	Intermediate	7	22
	Low	8	25
Relapse	Positive	9 high risk	37.5
		3 intermediate risk	
	Negative	8 low risk	62.5
		4 intermediate risk	
		8 high risk	
Postoperative treatment	No	12	37.5
	Yes	20	62.5
Her2/neu	Positive	14	43.7
	Negative	18	56.3
Total		32	100

(due to comorbid diseases) or difficulty to reach the patient, and so they were all excluded from the study. The remaining 32 cases were followed up for the following 2 years.

The patients' data and clinical presentation

Patients' demographic data revealed that 17 (53.1%) were men and 15 women (46.9%), with a male to female ratio of 1.1. The mean age was 63.4 (range: 39–88) years (Table 1).

Clinical data revealed that the most common presenting symptoms were vague abdominal pain in 17 patients (53%), followed by abdominal mass and melena (each was 40%); 6 patients (19%) were operated urgently due to severe upper gastrointestinal bleeding. The commonest presenting site was the stomach (31.3%).

Surgical workup

A total of 10 patients presented with gastric GISTs: 7 of them underwent partial and 3 total gastrectomies; 4 cases with

duodenal GISTs underwent urgent pylorus-preserving pancreaticoduodenectomies due to an ulcerated mass located near the ampulla of Vater; 1 case presented with GIST in the fourth part of duodenum—the patient underwent local resection and duodenojejunostomy; 7 cases with ileal, 5 with jejunal, and 3 with colonic GISTs underwent segmental resection and anastomoses; one case with cecal GIST underwent right hemicolectomy and another with rectal GIST underwent abdominoperineal resection (Table 1).

Histopathologic and immunohistochemical results

Histopathologic data revealed that 17 cases had high-risk (53%), 7 had intermediate-risk (22%), and 8 had low-risk tumors (25%). Furthermore, microscopic examination revealed spindle cell configuration in 20 tumors (62.5%), epithelioid in 8 (25%), and mixed differentiation in 4 (12.5%) (Table 1, Figure 1).

The Her2/neu immunohistochemical expression was negative in 18 cases of GISTs (56.2%). Conversely, it was expressed

in 14 cases (43.8%), independent of their localization and the risk of aggressive behavior (Table 1, Figure 2).

Follow-up outcome

Imatinib therapy was initiated in 20 patients: 17 patients represented the high-risk group, as recommended by most of the treatment protocols, and 3 represented the intermediate-risk

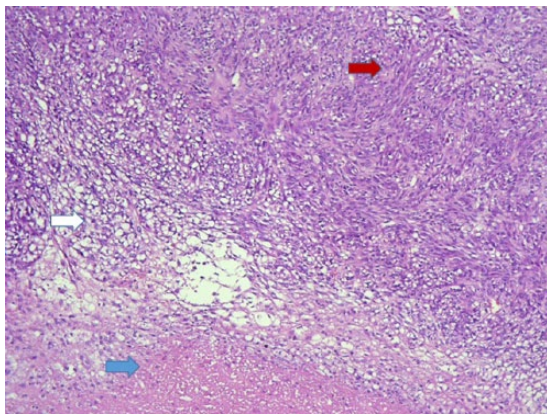


Figure 1. High-grade mitotically active gastrointestinal stromal tumor showing mixed type of epithelioid (white arrow) and spindle cell differentiation (red arrow) together with focal area of tumor necrosis (blue arrow) (hematoxylin-eosin, original magnification $\times 100$).

group in whom tumors were arising from ileum as they are usually associated with less favorable outcomes³ (Table 1).

Postoperative recurrence of the disease occurred in 12 patients (45% of all treated cases): 9 were of high-risk group and 3 were of intermediate group who did not receive postoperative imatinib. The relapse was presented in the form of liver metastases in 4 cases and local tumor recurrence in 8 cases. The remaining 20 patients (62.5%) (8 patients with low-risk, 4 with intermediate-risk, and 8 with high-risk tumors) were free of recurrence all through the follow-up period (Table 1).

Statistical relationships

In a statistical analysis of the Her2 expression, it was significantly correlated with increased risk grade of the GISTs ($P = .04$), tumor size ($P = .001$), mitotic count ($P = .00$), and tumor relapse ($P = .00$) (Table 2).

In a statistical analysis of tumor relapse, it was significantly correlated with the tumor mitotic count ($P = .00$) and risk grade ($P = .04$), but not with tumor size ($P = .2$) and postoperative imatinib treatment ($P = .3$) (Table 3).

Using the kappa agreement test, it showed that the cutoff value was 4 mitotic counts/50 HPF with which the tumor might be associated more with relapse, with 83% sensitivity, 70% specificity, and P value of .003 (Figure 3).

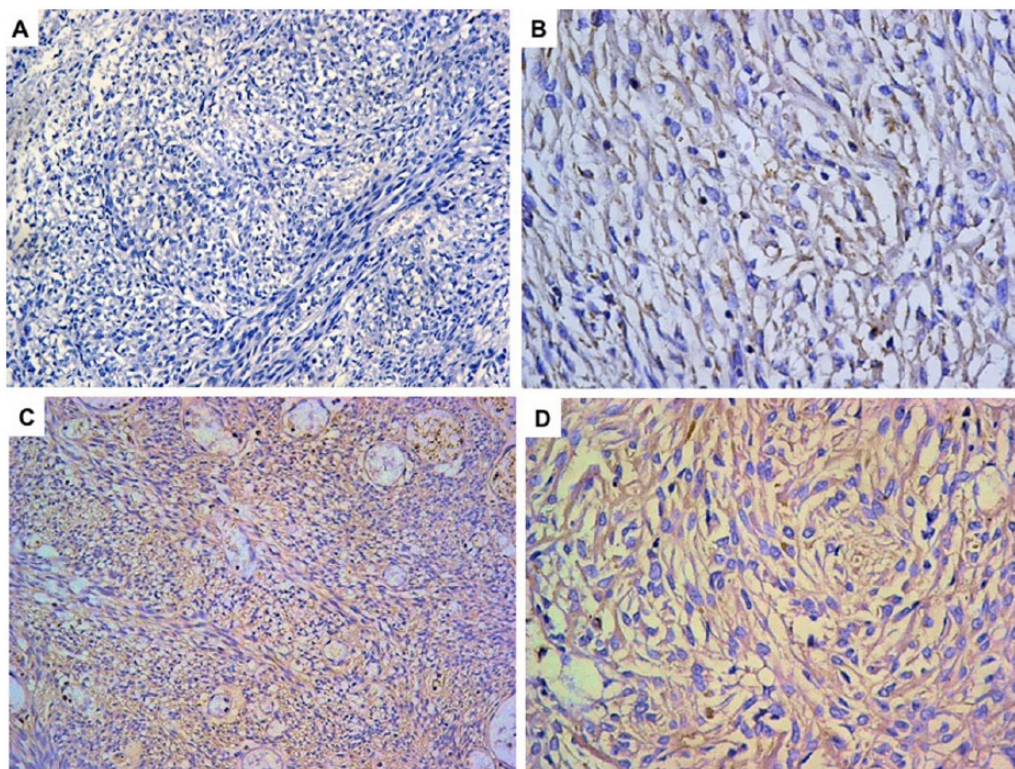


Figure 2. (A) Intermediate-grade gastrointestinal stromal tumor (GIST) with mixed epithelioid and spindle cell differentiation showing negative Her2 staining (Her2/neu, original magnification $\times 200$). (B) Low-grade GIST with epithelioid cell differentiation showing weak, incomplete membranous Her2/neu staining (Her2/neu, original magnification $\times 400$). (C) High-grade GIST with mixed epithelioid and spindle cell differentiation showing strong positivity to Her2/neu immunohistochemical staining (Her2/neu, original magnification $\times 200$). (D) High-grade GIST showing strong positivity to Her2/neu immunohistochemical staining (Her2/neu, original magnification $\times 400$).

Table 2. Statistical correlation between Her2/neu immunohistochemical staining and tumor clinicopathologic features (size, risk group, mitotic count, and relapse).

VARIANTS	HER2/NEU SCORE			χ^2	P VALUE
	0/1+	2+	3+		
	NEGATIVE	WEAK POSITIVE	POSITIVE		
Tumor size, cm^a					
<5 (1, 11%)	8 (89%)	0	1 (11%)	10.2	.001**
5-10 (6, 54.5%)	5 (45.5%)	2 (18.1%)	4 (36.4%)		
>10 (7, 58.3%)	5 (41.7%)	3 (25%)	4 (33.3%)		
Risk group^a					
High (11, 64.7%)	6 (35.3%)	4 (23.5%)	7 (41.2%)	10.2	.04*
Intermediate (3, 42.9%)	4 (57.1%)	2 (28.6%)	1 (14.3%)		
Low (0)	8 (100%)	0	0		
Mitotic count/50 HPF^a					
<4 (1, 6.7%)	14 (93.3%)	1 (6.7%)	0	8.7	.00**
>4 (13, 76.5%)	4 (23.5%)	5 (29.4%)	8 (47.1%)		
Relapse^a					
Negative (2, 10%)	18 (90%)	1 (5%)	1 (5%)	24.7	.00**
Positive (12, 100%)	0	5 (41.7%)	7 (58.3%)		

Abbreviation: HPF, high-power fields.

^aTotal number and percentage of patients stained positive with Her2/neu.

*Significant.

**Highly significant.

Table 3. Statistical correlation regarding relapse with age of patients, tumor size, mitotic count, risk groups, and intake of postoperative imatinib treatment.

	RELAPSE		χ^2	Z	P VALUE
	POSITIVE	NEGATIVE			
	(12)	(20)			
Age, y	48.8 ± 19.1	51.4 ± 12.6			.7
Size, cm	13.8 ± 7.1	9.5 ± 9.1		1.4	.2
Mitotic count/50 HPF	11.3 ± 4.5	4.2 ± 4.7		4.2	.00**
Risk groups (No. of patients)					
High (17)	9 (53%)	8 (47%)	6.6		.04*
Intermediate (7)	3 (43%)	4 (57%)			
Low (8)	0	8 (100%)			
Postoperative treatment					
Yes (20)	9 (45%)	11 (55%)	1.3		.3
No (12)	3 (25%)	9 (75%)			

Abbreviation: HPF, high-power fields; z, Mann-Whitney.

*Significant.

**Highly significant.

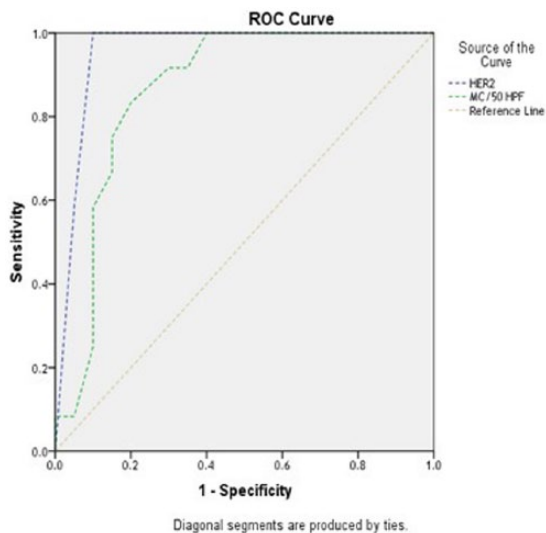


Figure 3. ROC curve showing the cutoff mitotic value (4/50 HPF) in GIST associated with higher incidence of relapse with 83% sensitivity, 70% specificity, and P value of .003. GIST indicates gastrointestinal stromal tumor; HPF, high-power fields; ROC, receiver operating characteristic.

Discussion

Some authors claimed that virtually all GISTs have the potential for malignant behavior, even those of 2 cm size or less with bland histologic features; thus, it is not appropriate to define any GIST as a benign tumor. The most reliable prognostic factors for GISTs are tumor size and the mitotic indices.^{14,15}

In this study, we have noted that Her2/neu immunohistochemical expression is significantly correlated with increased risk grade of the GISTs ($P = .04$), tumor size ($P = .001$), mitotic count ($P = .00$), and tumor relapse ($P = .00$). However, the relapse of the GIST shows a significant correlation with increased tumor risk ($P = .04$) and the tumor mitotic count ($P = .00$), which reveals a cutoff value of 4/50 HPF by kappa agreement analysis test.

It is interesting to find whether these results can be correlated; the aggressive biological behavior in these tumors may be attributed to Her2/neu gene amplification that makes an excess of the Her2 protein which promotes cancer cell growth and proliferation, and so Her2-positive tumors tend to be more aggressive than Her2-negative ones.¹⁶

Regarding the incidence of tumor relapse among our recruited patients and its relation to intake of postoperative imatinib, it was found that 45% of all treated cases experienced relapse during the 2-year follow-up. It is well known that the efficacy of imatinib, a CD117 inhibitor, is determined by the mutation status of CD117.¹⁷ When the mutation occurs in exon 11 (as is the case in most of the GISTs), the tumors would be responsive to imatinib. However, if the mutation occurs in exon 17 (as is often the case in seminomas and leukemia), the receptor is not inhibited by imatinib.¹⁸ Moreover, one study of GIST recurrence following surgery showed that although imatinib is effective against GIST, acquired drug resistance remains an important clinical challenge. Some patients present

with secondary imatinib resistance, which limits the prognostic outcome after resection of the tumor. The ideal duration of adjuvant treatment after surgery is still controversial.¹⁹

The short time of follow-up in our study has limited the results of 5-year survival rate. Strengths of the study are the cohort design through which we followed up the recruited cases; the stratification of the tumors according to the risk potentials gave more powerful statistical correlations. To the best of our knowledge, our study is the first to design a research that correlates Her2/neu with GIST.

In this study, slight male predominance is observed, which is comparable with results of some authors,²⁰ although others showed an equal male to female ratio or even a slight female predominance²¹; this difference can be attributed to the sample size.

The mean age of our recruited cases is 62.5 years, which is comparable with a study made by Koay et al,²² in which the sample age ranged from 59.2 to 63 years. The tumor site predominance, stomach and small intestine, is in accordance with other studies.^{13,20} Most of our cases are in high-risk category; this result is similar to a study by Orosz et al.²⁰

Regarding the correlation of Her2/neu with GIST mitotic count, risk grade, and tumor size, it is found that Her2/neu is more expressed in mitotically active, high-grade, large-sized tumors (>5 cm in diameter and mitotic count >4/50 HPF) with a significant predictive value (.00, .04, and .001, respectively); these are in accordance with the findings of many research works which found a strong association between Her2/neu staining and advanced stage and grade of breast cancer.²³⁻²⁶

The relationship between Her2 expression and relapse in patients with GIST was very interesting; Her2/neu was expressed positively in all cases who experienced relapse within 2 years of follow-up, whereas it was positive in only 10% of cases who showed no relapse. This correlation was highly significant ($P = .00$). Our finding is in agreement with Slamon et al,²⁷ who declared the prognostic value of Her2 expression in breast cancer relapse and survival. But it was different from Zurawska et al²⁸ who found that patients with early-stage breast carcinoma, who were positive for Her2/neu and negative for hormonal receptors or negative for Her2/neu and positive for hormonal receptors had similar outcomes, while triple negative cases experienced a significantly worse prognosis regarding the overall survival and relapse-free survival.

Analysis of the relationship between mitotic count and relapse in this study revealed that increased mitotic count of GIST tumor was significantly associated with the increased risk of tumor relapse after complete resection with cutoff value of 4/50 HPF (83.3% sensitivity, 70.0% specificity, and P value of .00). However, there was no significant correlation between incidence of relapse and tumor size ($P = .2$). Our results are in agreement with some researchers who indicated that the mitotic rate (index) might be more influential in predicting recurrence of GIST than risk grade. They added that some

slow-growing tumors could reach large sizes without becoming aggressive.²⁹

Our study proposed a cutoff value of mitotic count (4/50 HPF) that might be associated with increased risk of tumor relapse. Other researchers who studied mostly low-risk group patients reported 10 mitotic counts as a cutoff prognostic value.²⁹ This difference can be explained by the risk grade of the enrolled cases; most of our recruited cases were high-risk group with high mitotic counts that affected the statistical correlation.

Recently, there is also evidence that Her2 is an important biomarker in gastric and gastroesophageal junction tumors; it is now recommended that all patients with gastric adenocarcinoma should have their tumors tested for Her2 status at the time of initial diagnosis. Moreover, in the United States, trastuzumab is recommended for patients with Her2-positive metastatic adenocarcinoma of the stomach or gastroesophageal junction and in Japan for patients with inoperable advanced or recurrent Her2-overexpressing tumors.¹¹

These results might be of clinical significance to determine the tumor prognosis regarding the chance of relapse. However, more research works with greater sample size and longer follow-up period are recommended especially if correlated with Her2 gene amplification using fluorescence in situ hybridization assay.

Conclusions

Her2/neu immunohistochemical staining of GIST might be of help as a prognostic marker to determine how aggressive the tumor is likely to be, to suggest the treatment options, and to understand more about the tumor's characteristics. Moreover, the cutoff value of mitotic count that might predict tumor relapse is 4/50 HPF.

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The authors alone are responsible for the content and writing of the paper.

Author Contributions

AMA, AA, ME and EAI conceived and designed the research. AMA and EAI collected the data. AMA, AA, EAI, ZML and SAS analyzed the data. EAI and SAS made the histopathological scoring. EAI wrote the first draft of the manuscript. AMA, ZML and SAS contributed to the writing of the manuscript. AMA, EAI and SAS jointly developed the structure and argument of the manuscript. All the authors agreed with manuscript results and conclusion, made the critical revisions and approved the final version.

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