Comparative study between c-kit and DOG-1 immunohistochemical expression in GISTs

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Abstract: The diagnosis of GISTs shows controversy in their diagnosis, so pathologists commonly employ a panel of immunohistochemical markers. However, making the diagnosis can be difficult for the c-kit negative cases and c-kit positive cases that exhibit the same morphological pattern of other mesenchymal tumors and also stain c-kit positive. This work aimed to compare between the immune-histochemical expression of c-kit and DOG-1 and their diagnostic efficacy in GISTs using the percentage ratio score and intensity score. **Results;** Out of the 70 cases, only 54/70 cases were positive in both markers, 4/70 cases were negative for c-kit. Those cases were stained by other markers as (SMA and CD34) to confirm the diagnosis, resulting that, the c-kit negative cases considered as GISTs. Immunohistochemical results of c-kit revealed significant co-relation between the marker percentage score with WHO classification, and stage. Also, significant co-relation between the marker intensity with cell type, WHO classification and stage was detected. Immunohistochemical results of DOG-1 revealed significant co-relation between the marker percentage score with WHO classification, but, no significant association with stage. On the other hand, significant co-relation between the marker intensity with WHO classification and stage was detected. Significant co-relation between c-kit intensity and DOG-1 intensity were noticed but no significant co-relation between c-kit ratio score and DOG-1 ratio score. **Conclusion:** Both the sensitivity and specificity of DOG-1 were 100% compared to 93.10% and 66.67% of c-kit, respectively. DOG-1 have diagnostic accuracy 100% compared to 82.98% for c-kit. These results may magnify the importance of DOG-1 in that may be able to pick up a large numbers of c-kit negative cases and diagnose them as GIST. DOG1 immune-staining in mesenchymal tumors could be one of the best recommended markers to differentiate between GISTs & other tumors.
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Key words: GIST, c-kit, DOG-1

1. Introduction:

Gastro-intestinal stromal tumors (GIST) constitute 1-3% of all gastrointestinal malignancies and is the most common mesenchymal tumor of the gastrointestinal tract *(Zhong et al., 2013).* Relative incidence in Egypt about 2.5% of all gastrointestinal tumors and 0.3% of all malignancies. They arise from interstitial cells of Cajal (ICC) or their stem cell precursors which are normally are part of the autonomic nervous system of the intestine and serves as a pacemaker function in controlling motility *(Nakhla et al., 2012).* GISTS can occur anywhere along the digestive tract but are most commonly arise from the stomach, closely followed by the small bowel. They are uncommon in the large bowel and rectum and rare in the esophagus *(Liegl et al., 2009).* Subsequent studies have confirmed that 85% to 90% of GISTs have activating mutations in KIT or the homologous RTK platelet derived growth factor receptor alpha (PDGFRA) gene *(Heinrich et al., 2003[a] and Heinrich et al., 2003[b]).* C-kit protein (CD117) has been shown to be a relatively specific immunohistochemical marker for GIST *(Medeiros et al., 2004).* Pathological diagnosis of GISTs is based on histological findings and immunohistochemical demonstration of the c-kit protein *(Kang et al., 2011).* Until recently, c-kit immunohistochemistry has been the main tool for the verification of GIST. The problems in the current immunohistochemical identification of GIST include c-kit negative GISTs *(Lasota et al., 2008).* C-kit-negative GISTs account for about 5% of cases and cause diagnostic difficulties. A correct diagnosis of GISTs is important for therapeutic reasons regardless of c-kit expression *(Kang et al., 2011).* Recent studies have suggested that antibodies against DOG-1(Discovered on GISTs-1) have superior sensitivity and specificity compared with c-kit, and that these antibodies could serve as specific immunohistochemical markers for GIST (*Espinosa et al., 2008 and Jung et al., 2011).* DOG-1 antibodies are more sensitive than KIT antibodies in detecting tumors of gastric origin, tumors with epithelioid morphology, and tumors harboring PDGFRA mutation. Furthermore, DOG-1 immunoreactivity is rarely observed in other mesenchymal and non mesenchymal tumor types *(Lee et al., 2010).* The high expression of DOG-1 in GISTs indicates its importance in the tumorigenesis and tumor developments, and DOG-1 may be a potential marker for tumor diagnosis. The high sensitivity and

specificity makes DOG-1 an important diagnose evidence *(Sun et al., 2012).*

This work aimed to compare the sensitivity and specificity of DOG-1 with that of c-kit in gastrointestinal stromal tumors and to define the diagnostic utility of both DOG-1 and c-kit in gastrointestinal stromal tumors using the collected data.

2. Material and methods

This retrospective study was performed on paraffin blocks of 70 cases of Gastro-intestinal stromal tumor specimens of Egyptian patients, obtained during the period between 2008 to 2015. These cases were previously diagnosed as GIST by relative histo-pathological examination using ordinary hematoxylin and eosin stains (H&E) and clinical data. All cases were obtained from Pathology Department -Faculty of medicine -Tanta University, Pathology Department-Tanta Cancer Centre and Private laboratories.

2.1 Histopathological study; paraffin blocks of cases were cut by ordinary microtone to usual histologic sections 3-5 micron in thickness for H&E staining. Cases were reviewed for definite tumor cell typing (spindle, epithelioid, or mixed), tumor cellularity, nuclear atypia (mild, moderate and marked according to (Strickland et al., 2001), necrosis, mitotic rate [expressed as the number of mitotic figures/ 50 high-power fields (HPFs) in the most mitotic area, using a 40 objective and a 10 ocular; field size 0.25mm^2]. Grading was done according to WHO grading system (2000), risk stratification was performed according to the NIH risk table of GIST (Joensuu, 2008) and staging of cases was done according to AJCC (2010) as published in the work Demetri et al. (2010).

2.2 Immunohistochemical staining:

Immunohistochemical staining was performed using the streptavidin-biotin immunoperoxidase technique. The UltraVision Detection Kit (TP-015-HD, Lab Vision, USA) was used according to the manufacturer's protocol. The used primary antibodies included:

Rabbit polyclonal antibody (c-kit antibody, #A4502), used at dilution 1:200 and obtained from DakoCorporation. Positive control is GIST. Rabbit monoclonal antibody (DOG-1 antibody, # SP31), used at dilution 1:50 and obtained from Lab Vision Corporation. Positive control is GIST. Each staining run included both external positive and negative control slides to confirm that the correct procedure has been followed and the staining system worked properly. Incubation period was over night at room temperature for both markers. Negative controls were prepared by omission of the primary antibodies.

2.2. a Interpretation of immunohistochemical staining:

2.2. b Evaluation of both c-kit immune-staining and DOG-1: Expression was assessed in both the cytoplasm and the cyto-membrane. The scoring systems were performed according to:

1- **Liegl *et al., (2009)***: subdividing positive cells into five categories:

Score 0: no staining, score 1+: the number of positive cells < 5%, score 2+: the number of positive cells 5%-25%, score 3+: the number of positive cells 25%- 50%, score 4+: the number of positive cells >50%. S.

2- **Kang *et al*., *(2011):*** intensity were classified into four categories: Negative, weak, moderate, and strong.

3- **El Rebey and Aiad, (2014)**: comparing expression of dog1 and c-kit scores with clinico-pathologic parameters were lumped together as low scores (scores 0, 1, 2) and high scores (scores 3, 4) for statistical purpose.

2.3 Statistical presentation and analysis of the present study was conducted using the Statistical Package of Social Sciences (SPSS Inc., Chicago, Illinois, USA) software for windows, version V.20. The mean, standard deviation, chi-square test, analysis of variance (ANOVA) tests (f), and linear correlation coefficient (r) were calculated. Differences were considered significant when *P*-value was < 0.05.

3. Results:

3.1 Histopathological results:

According to the morphologic features of GIST there were 44/70 lesions (63%) of spindle cell type, included [Hypercellular spindle cell, Palisaded and vacuolated spindle cell, signet ring cell type**,** Sarcomatous spindle cell, Sclerosing spindle cell, gastrointestinal autonomic nerve tumors (GANT)**].** 14/70 lesions (20%) of epithelioid cell type, included [hypercellular epithelioid, Sarcomatous epithelioid and cytotoxic T-lymphocytes rich GIST] and 12/70 lesions (17%) of mixed type, included [GISTs with a rhabdoid cells**.** Out of the 70 cases there were 30/70 cases (43%) showed mitotic activity ≤5/50 hpf included cases with no mitotic activity and 40/70 lesions (57%) showed mitotic activity >5/50 hpf. Also, 14/70 cases (20%) showed distant metastasis mainly to liver and 2/70 cases (3%) showed nodal metastasis**.**

The studied cases of GIST were classified according to the WHO classification (2000) and Joensuu 2008 risk stratification system as shown in diagrams,1-2. Then they were categorized according to AJCC (2010) as shown in diagram-3.

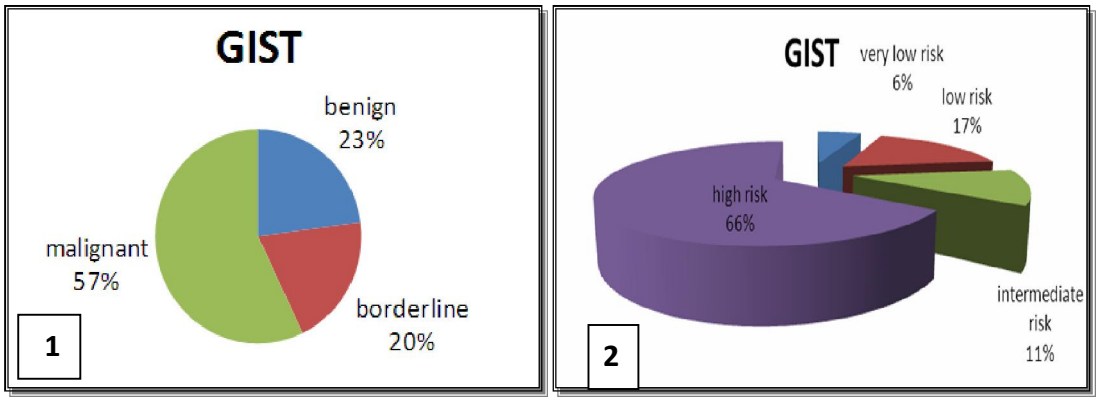


Diagram-1: WHO classification of studied cases.
Diagram-2: Risk stratification of studied cases

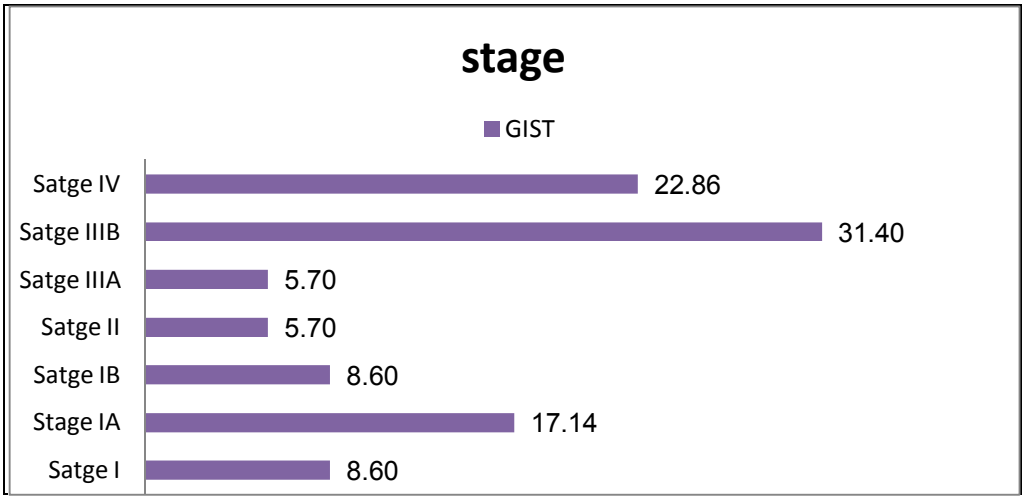


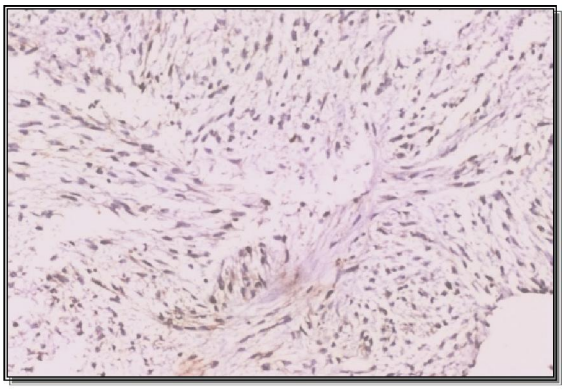
Diagram-3: Staging of studied cases

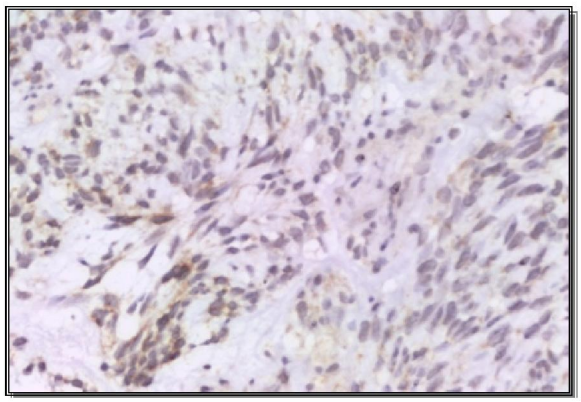
3.2 Immunohistochemical results:

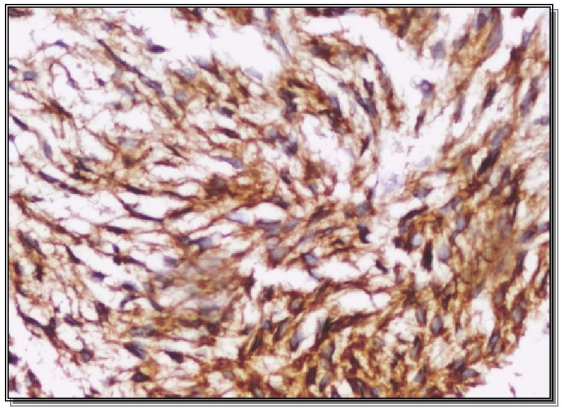
Table-1: Immunohistochemical expression of c-kit and DOG-1 in the studied GISTs

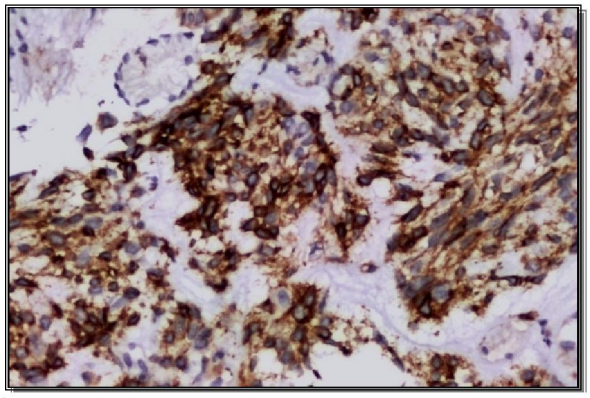
Item		GIST		Item		GIST	
		No.	%			No.	%
C-kit	Negative	4/58	6.90	**DOG-1**	Negative	0/58	0.00
	Positive	54/58	93.10		Positive	58/58	100.00
C-kit staining ratio score	Low (0,1,2)	12/58	20.69	**DOG-1 staining ratio score**	Low (0,1,2)	6/58	10.34
	High (3,4)	46/58	79.31		High (3,4)	52/58	89.66
C-kit staining intensity	Negative	4/58	6.90	**DOG-1 staining intensity**	Negative	0/58	0.00
	Weak	10/58	17.24		Weak	6/58	10.34
	Moderate	30/58	51.72		Moderate	12/58	20.69
	Strong	14/58	24.14		Strong	40/58	68.97

After using the immunohistochemical markers (c-kit and DOG-1) on the 70 cases which previously diagnosed as GISTs by H&E and clinical data, it was founded that 54/70 cases ***only*** were positive for both markers, Those negative cases either for c-kit or DOG-1 were stained by other markers as (SMA & CD34) for confirming the diagnosis, resulting that four cases showed positive reaction for SMA &/ or CD34 and so, they were considered as GISTs**.** The remaining 12 cases showed negative reaction for SMA and CD34,









intensity (Immunoperoxidase X 200).

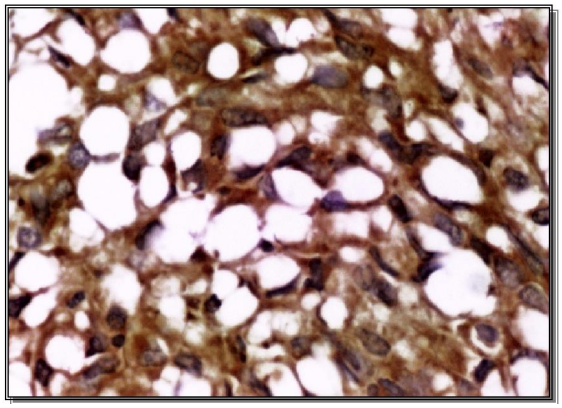


Fig. 3-a: Malignant GIST (signet ring variant) showing cytoplasmic positivity for C-KIT Score (4+) /strong intensity (Immunoperoxidase X 400).

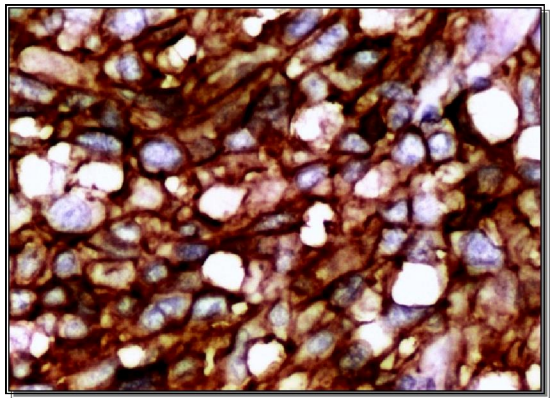


Fig. 3-b: Same case showing membranous positivity for DOG1 Score (4+) /strong intensity (Immunoperoxidase X 400).

3.3 Comparison between c-kit& DOG1 expression in GISTs

Out of 58 GIST cases, all the 54 c-kit-positive tumors also expressed DOG-1 positive. **According to the staining score (Table-2),** out of 46 cases of high score c-kit, (42 cases expressed high score DOG-1 and 4 cases expressed low score Dog-1). While, out of the 12 cases with low score c-kit (10 cases expressed as high score DOG-1). **And, according to the staining intensity (Table-3),** out of 10 cases of weak staining c-kit, (2 cases showed strong DOG-1 stain, 6 cases showed moderate DOG-1 stain and 2 cases showed weak DOG-1 stain), out of 30 cases of moderate staining c-kit, (24 cases showed strong DOG-1 stain, 4 cases showed moderate DOG-1 stain and 2 cases showed weak DOG-1 stain) and all 14 cases of strong staining c-kit showed strong DOG-1 stain. On the other hand, all the fourc-kit negative tumors expressed DOG-1 positive. **According to cell type (Table-4);** All epithelioid cell lesions 12/12 stained with high score DOG-1 and c-kit, all mixed cell lesions 10/10 stained with high score DOG-1, and all lesions stained with low score DOG-1were spindle cell type**. According to WHO classification (2000, Table-5);** All borderline GISTs were strong DOG1. Most of malignant GISTs were strong DOG1 (26/34), but only eight cases of them were strong c-kit. Co-relations between WHO prognostic group and c-kit or DOG1 immune-staining intensity were significant as *P* value < 0.05. **According to risk stratification (Table-6);** All very low risk GISTs were low c-kit score, but high DOG-1 score. All intermediate GISTs were high c-kit score and high DOG1 score. Co-relations between risk stratification and C-kit or DOG1 immune-staining ratio score were significant as *P* value < 0.05. **According to the stage of studies GISTs (Table-7);** Most of cases at all stages expressed with high score c-kit except cases staged l A, most of them expressed with low score c-kit. Also, cases at all stages expressed with high score DOG1 but 50% of cases staged l expressed with high score DOG1 and the other 50% expressed with low score. Significant co-relation between stage and c-kit immune-staining ratio score was detected as *P* value <0.05, but no significant co-relation between stage with DOG1 immune-staining ratio score as *P* value >0.05.

Table-2: Comparison between c-kit and DOG1 ratio score expression in studied GISTs.

DOG-1 staining ratio	C-kit staining ratio						chi-square	
	Low (0,1,2)		High (3,4)		Total			
	N	%	N	%	N	%	X^2	*P*-value
Low (0,1,2)	2	3.45	4	6.90	6	10.34	0.59	0.443
High (3,4)	10	17.24	42	72.41	52	89.66		
Total	12	20.69	46	79.31	58	100.00		

Table-3: Comparison between c-kit and DOG1 staining intensity in studied GISTs.

DOG-1 staining intensity	C-kit staining intensity									
	Negative		Weak		Moderate		Strong		Total	
	N	%	N	%	N	%	N	%	N	%
Negative	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Weak	2	3.45	2	3.45	2	3.45	0	0.00	6	10.34
Moderate	2	3.45	6	10.34	4	6.90	0	0.00	12	20.69
Strong	0	0.00	2	3.45	24	41.38	14	24.14	40	68.97
Total	4	6.90	10	17.24	30	51.72	14	24.14	58	100.00
chi-square	X^2		32.549							
	P-value		0.000*							

Table-4: Co-relation between c-kit & DOG1 ratio score expression and cell type.

C-KIT staining ratio	Histological cell type						Chi-square	
	Spindle		Epithelioid		Mixed			
	N	%	N	%	N	%	X^2	*P*-value
Low	8	66.67	0	0.00	4	33.33	7.540	0.023*
High	28	60.87	12	26.09	6	13.04		
Total	36	62.07	12	20.69	10	17.24		
DOG-1 staining ratio	N	%	N	%	N	%	X^2	*P*-value
Low	6	100	0	0.00	0	0.00	6.141	0.046*

Table-5: Co-relation between c-kit & DOG1 staining intensity with WHO classification.

C-KIT staining intensity	WHO classification						Chi-square	
	Benign		Borderline		Malignant			
	N	%	N	%	N	%	X^2	*P*-value
Negative	2	50.00	0	0.00	2	50.00	21.496	<0.001*
Weak	6	60.00	0	0.00	4	40.00		
Moderate	6	20.00	4	13.33	20	66.67		
Strong	0	0.00	6	42.86	8	57.14		
DOG1 staining intensity	N	%	N	%	N	%	X^2	*P*-value
Negative	0	0.00	0	0.00	0	0.00	18.453	<0.001*
Weak	4	66.67	0	0.00	2	33.33		
Moderate	6	50.00	0	0.00	6	50.00		
Strong	4	10.00	10	25.00	26	65.00		

Table -6: Co-relation between C-KIT& DOG1 ratio score expression and risk stratifications.

	Risk stratification									
	Very low risk		Low risk		Intermediate risk		High risk		Chi-square	
C-KIT staining ratio	N	%	N	%	N	%	N	%	X^2	*P*-value
Low	4	33.33	4	33.33	0	0.00	4	33.33	20.562	<0.001*
High	0	34.78	6	13.04	8	17.39	32	69.57		
Total	4	6.90	10	17.24	8	13.79	36	62.07		
DOG-1 staining ratio	N	%	N	%	N	%	N	%	X^2	*P*-value
Low	0	0.00	4	66.67	0	0.00	2	33.33	9.672	0.022*
High	4	7.69	6	11.54	8	15.38	34	65.38		
Total	4	6.90	10	17.24	8	13.79	36	62.07		

Table-7: Co-relation between c-kit& DOG1 ratio score expression with stage.

C-KIT stain ratio	Stage													
	Stage I		Stage IA		Stage IB		Stage II		Stage IIIA		Stage IIIB		Stage IV	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Low score	0	0.00	8	66.67	0	0.00	0	0.00	0	0.00	2	16.67	2	16.67
High score	4	8.70	4	8.70	6	13.04	2	4.35	2	4.35	16	34.78	12	26.09
Total	4	6.90	12	20.69	6	10.34	2	3.45	2	3.45	18	31.03	14	24.14
chi-square	X^2				19.821									
	P-value				0.003*									
DOG1 stain	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Low score	2	33.33	2	33.33	0	0.00	0	0.00	0	0.00	2	33.33	0	0.00
High score	2	3.85	10	19.23	6	11.54	2	3.85	2	3.85	16	30.77	14	26.92
Total	4	6.90	12	20.69	6	10.34	2	3.45	2	3.45	18	31.03	14	24.14
chi-square	X^2				9.664									
	P-value				0.140									

3.4 Diagnostic efficacy of c-kit & DOG1 in GISTs (Tables 8&9); As regards to c-kit immune staining results, the PPV for the diagnosis of GIST was 81.82%. The NPV was 85.71%. The overall diagnostic accuracy was determined to be 82.98%, with a sensitivity and specificity of 93.10 % and 66.67 % respectively. And for DOG1, the PPV for the diagnosis of GIST was 100%. The NPV was 100 %. The overall diagnostic accuracy was determined to be 100 %, with a sensitivity and specificity of 100 % for both.

Table-8: Diagnostic efficacy of c-kit.

C-kit	Type of tumor						Chi-square	
	GIST		Control group		Total			
	N	%	N	%	N	%	X^2	*P*-value
Negative	4	6.90	24	66.67	28	29.79	39.562	<0.001*
Positive	54	93.10	12	33.33	66	70.21		
Total	58	100.00	36	100.00	94	100.00		

Sens.	Spec.	PPV	NPV	Accuracy
93.10	66.67	81.82	85.71	82.98

Table-9: Diagnostic efficacy of DOG-1.

DOG-1	Type of tumor						Chi-square	
	GIST		Control group		Total			
	N	%	N	%	N	%	X^2	*P*-value
Negative	0	0.00	36	100.00	36	38.30	125.115	<0.001*
Positive	58	100.00	0	0.00	58	61.70		
Total	58	100.00	36	100.00	94	100.00		

Sens.	Spec.	PPV	NPV	Accuracy
100	100	100	100	100

4. Discussion:

In Egypt, GISTs represent 5.77%, 1.88% and 2.06% of gastric, colonic and anorectal malignant tumors respectively *(Mokhtar et al., 2007)*.

Histologically, GISTs demonstrate considerable morphologic overlap with other tumors. In routine practice, the diagnosis of GISTs is based on the anatomic location of the tumor, histopathology and immunehistochemistry *(Abd El-Rehim and Gayyed, 2015)*. This study included 70 cases previously diagnosed as GISTs by H&E examination, but after immunohistochemistry staining 58 cases proved to be GISTs. Screening for c-kit mutations can be helpful in diagnosis of GISTs, but is needed to aid in routine diagnosis is a marker that reliably stains GISTs that are c-kit weak/negative *(El Rebey and Aiad, 2014)*. Hence, the use of another reliable, available immune histochemical marker, that is much less expensive than c-kit gene mutation analysis was unnecessary to achieve reliable, feasible, rapid and less expensive diagnosis *(Abdel-Hadi et al., 2009)*. DOG-1 is strongly expressed on the surface of the neoplastic cells irrespective of mutation status, being rarely expressed in other soft tissue tumors, as demonstrated by earlier studies. In the current study, c-kit negative cases represented in 6.90% and positive cases represented in 93.10%. These results are nearly similar with that done by *Heinrich et al. (2008)* which reported that between 5% and 10% of GISTs fail to immune-staining for c-kit, *Sözütek et al. (2014)* reported that c-kit was positive in (93.7%) cases and negative in (6.3%) cases, *Miettinen et al. (2009), Kang et al. (2010) and Sun et al, (2012)*studies shown c-kit positivity 94.7%, 89.8% and 90.48% respectively. While, DOG-1expressed in all studied cases of GISTs (100%). These results were in agreement with that done by *Fatima et al. (2011),* and nearly similar to that done by (97.5%) *West et al. (2004) and Nakhla et al.(2012)* who reported immunopositivity for DOG-1 in 97.5% and 97.4%respectively. Significant correlations between c-kit and DOG-1 expression with WHO classification of the studied GISTs (*P* value < 0.05) was reported in this study. In agreement to these results, *Abdel-Hadi et al. (2009*) reported that the high

c-kit immune-staining scores were significantly associated with high-risk tumors. On the contrary, *Kang et al. (2010)& El Rebey and Aiad,(2014*) reported that there is no significant correlation between c-kit or DOG-1 with risk stratification. In the current study, the intensity of staining for c-kit antibody in GISTs ranged from 6.90% of negative cases, 17.24% of weak staining cases, 51.72% of moderate staining cases to 24.14% of strong staining cases. On the contrary, the intensity of staining for DOG-1 antibody in GISTs was ranged from 10.34% weak staining, 20.69% moderate staining and 68.97% strong staining. *Nakhla et al. (2012*) study reported that, the intensity of positivity staining for c-kit antibody ranged from weakly positive in12.83%, moderately positive in 30.76% and strongly positive in 56.41% of cases. They reported intensity of positive staining for DOG-1 antibody ranged from weakly positive in 17.94%, moderately positive in 48.72% and strongly positive in 33.34%of cases. *Kang et al. (2011*) found that the overall staining intensity for DOG-1 was weak in 21%, moderate in 34% and strong in 36% of cases. *Sözütek et al. (2014)* study found that DOG1with weak stain in 36.5%, moderate stain in 36.5% and strong stain in 28% of cases. The differences between studies likely reflect among other factors, type of marker anti body and number of cases. Significant correlation between c-kit and DOG-1 expression in the studied cases with WHO prognostic groups (P value < 0.05). Significant correlation between c-kit and DOG-1 expression in the studied cases with stage (P value < 0.05), was detected. In the current study, the results demonstrated that DOG-1 is a specific and sensitive marker for GIST, as it stain all cases of GIST included in the study and didn't stain any of the other tumors tested. Immunohistochemical staining and diagnostic efficacy of DOG1was compared with that of c-kit in GISTs. DOG-1 proved to be a more specific (100% versus 66.67%) and more sensitive (100% versus 93.10%) marker than c-kit for the diagnosis of GISTs. In agreement to this study, *Espinosa et al. (2008)* demonstrated similarly superior sensitivity and specificity of these antibodies compared with KIT, DOG1 reactivity was seen in 87% of GIST cases, whereas the expression of KIT was found in 74%. *Fatima et al. (2011)* showed superior specificity and sensitivity for DOG-1 versus c-kit antibodies (100% versus 76%) and (100% versus 70%), respectively. *Abdel-Hadi et al. (2009)* showed specificity for DOG1 and c-kit antibodies (100% versus 81.8%), respectively. *El Rebey and Aiad, (2014)* showed sensitivity for DOG-1 versus c-kit antibodies (94.1% versus 68.6%), respectively.

Conclusion: DOG1 have diagnostic accuracy 100% compared to 82.98% for C-KIT. These results may magnify the importance of DOG1 in that may be able to pick up a large numbers of C-KIT-negative cases and diagnose them as GIST.

Conflict of interest:

There is no conflict of interest or financial ties to include.

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