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*Original Research Article.*

# GIST: A Study of Diagnostic and Predictive Factors in Reference to the Site

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## ABSTRACT

Gastrointestinal stromal tumors (GIST) are biologically distinctive stromal tumor and are the most common mesenchymal tumor of gastrointestinal tract but many times creates great clinical confusion due to its vivid clinical presentation, location and histology. Immunohistochemistry plays a great deciding role even in the era of molecular biology as around 90% GISTs are CD117 positive which represents the presence of KIT receptor (i.e. a 145-kDa glycoprotein) & is responsible for uncontrolled cell proliferation. Hence targeted therapy can be planned for all those cases with good clinical outcomes.

In the present study, we have considered various aspects of GIST including their size, histomorphological and immunohistochemical characteristics with their relevance in diagnosis and as predictive factor for risk management.

**Key-words:** GIST (Gastrointestinal Stromal Tumor), IHC, KIT, GIT, CD117, DOG1.

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## INTRODUCTION

Gastrointestinal stromal tumor (GIST) arises in the wall of gut and recapitulates the phenotype of interstitial cells of Cajal. GIST is the most common (80%), mesenchymal tumor of the alimentary canal.[1] It accounts for less than 1% of the entire gastrointestinal tumor and about 5% of all sarcomas[2] with an annual incidence of 11-14/per million.[3,4] GIST can occur throughout GIT and may have extra-intestinal involvement referred as EGIST. GIST commonly presents between 4$^{th}$ and 5$^{th}$ decade of life with median age of approximately 60 years.[5] Sometime GIST can present in paediatric population. Overall there is no sex predilection; however in specific clinical association such as those arising in the paediatric population, slight female predilection has been noted.[6-9] Only 70% of patients with GIST are symptomatic; rest (20%) remains asymptomatic and detected incidentally. 10% are only detected at autopsy.[10] GIST is well circumscribed tumor, most commonly arising in the muscularis propria of the GI tract. GIST varies greatly in size from few mm to more than 30 cm. Median size being 5 cm to 8 cm.KIT expression is a specific and sensitive marker for GIST within the standard differential diagnostic setting . Overall 90% of GIST are immunoreactive for KIT.[11] IHC for CD117 is positive in most of the cases. Vimentin and SMA are also positive in variable number of cases. DOG1 have similar sensitivity as CD117 for diagnosing GIST. In our study, we have tried to overview various aspects of GIST including their origin, site, size, morphology and immunohistochemistry characteristics and relevantly considered the diagnostic and predictive factors for the risk assessment.

## MATERIALS AND METHODS

This is a 54 months laboratory based prospective type descriptive study done in Department Of Pathology, SMS, Jaipur. From Jan 2011 to June 2016, total 48,000 surgical specimens were received in our department for histopathology. Out of which 480 cases (1%) were of suspected GI malignancy. The specimens received were taken by incisional either biopsy or radical surgery.

The specimen were fixed in 10% formalin overnight, grossed and processed in automated tissue processor. Routine Haematoxylin and eosin staining was performed. IHC was then applied on these tissue sections. The markers used were CD117, DOG1, S100, SMA, CD34, EMA.

## RESULTS

A total of 48000 specimens were received in our Department Of Pathology, SMS, Jaipur from Jan 11 to June 16 for histopathological examination. Out of these 480 (1%) cases were of GI malignancies & total 40 cases out of 480 malignancies (8.33%) were of Gastro Intestinal Stromal Tumors (GIST).

GIST are uncommonly seen in patients younger than 40 years and rarely seen in second decade (<1%). In our study age ranged from 19-70 years though majority of the cases were of middle to elderly age. The mean age in our study was 45 years. The age distribution as shown in Fig.1.

There was no sex predilection as almost equal numbers of cases were of male and female category. The most common site was small intestine followed by stomach and mesentry. Other sites

include colon, retroperitoneum, omentum, meckel's diverticulum, liver, upper chest wall and pelvic fossa mass. The percentage of cases in respective site mentioned in Fig.2.

The size of tumor was greatly variable, ranging from 6 mm to 22 cm. 31 cases had tumor size more than or equal to 5 cm and 9 /40 cases had tumor size less than 5 cm as shown in Fig.3. [5-10cm, 10 - 20 cm]. Mitotic activity less than 5/50 hpf seen in 16/40 cases (40%) and more than 5/50 hpf were seen in 24/40 cases (60%).Using tumor size, site and mitotic activity these GIST,s were categorized as very low risk, low risk, intermediate and high risk as depicted in Fig.4. CD117 positivity was seen in 36/40 cases (90%) and 4/40 cases (10%) were CD117 negative as depicted in Fig.5. All CD117 negative cases were DOG1 positive. Both were not concurrently negative in any of the case.

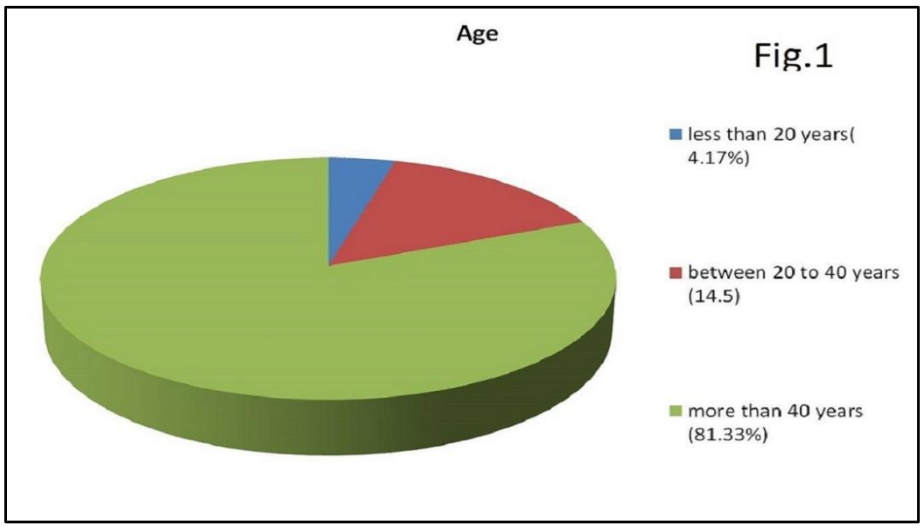


**Fig.1: Percentage of Age distribution of GIST cases.**

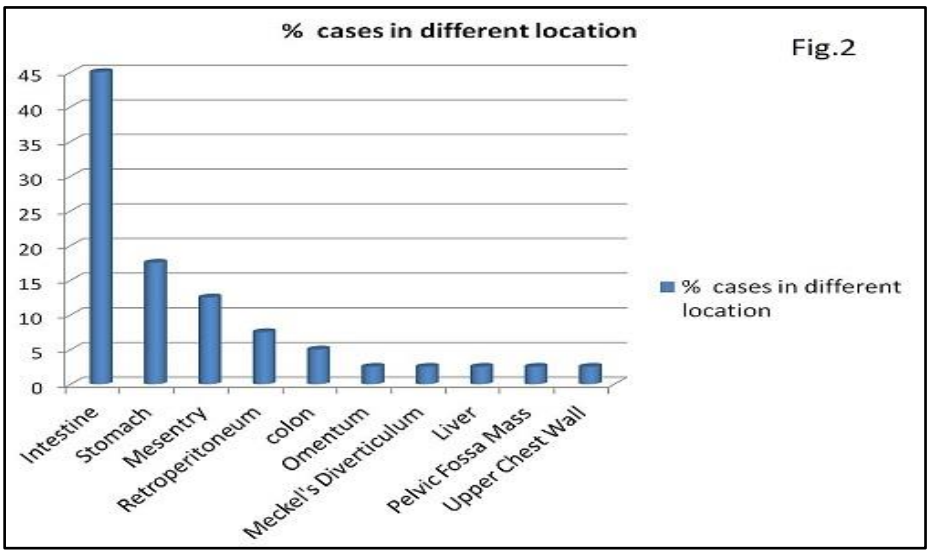


**Fig.2: Site distribution of GIST cases.**

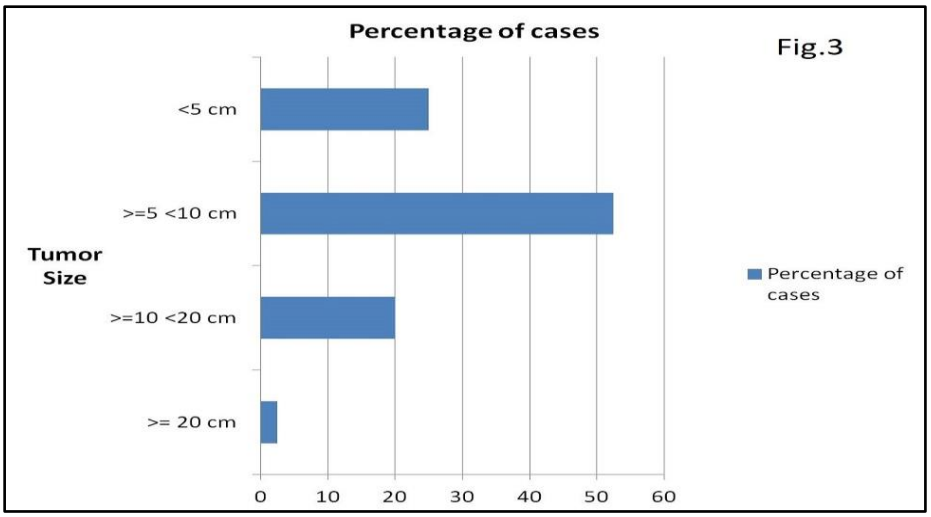


**Fig.3: Tumor Size Distribution.**

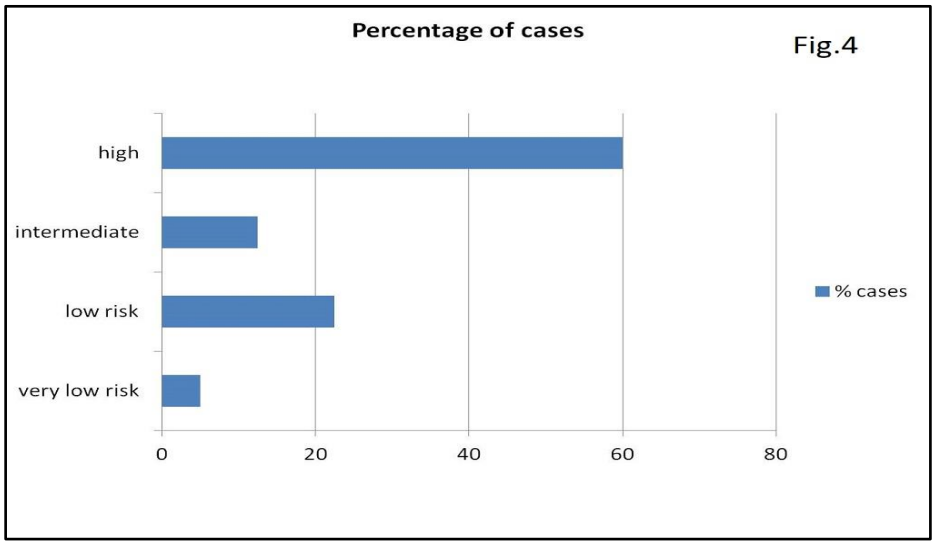


**Fig.4: Categorisation of GISTs cases according to their metastatic potential.**

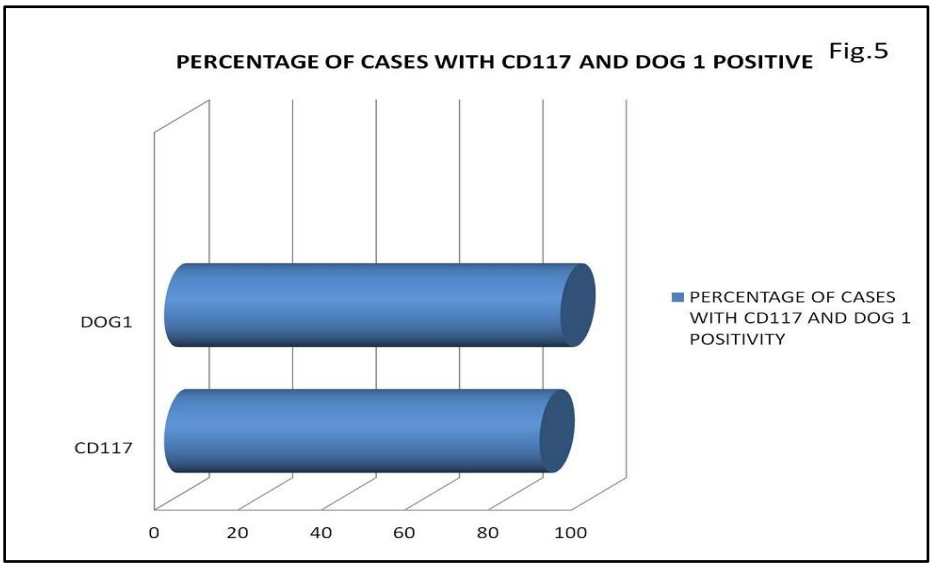


**Fig.5: Number of cases with CD117 and DOG1 positive.**

## DISCUSSION

GIST is the most frequent non epithelial tumor occurring in the stomach and small intestine. Despite numerous studies, GIST remains problematic with respect to its origin, differentiation, nomenclature and prediction of prognosis. GIST is defined as KIT or PDGFRA mutation derived mesenchymal tumor of the GI tract with specific histologic characteristic and include tumors which has a wide spectrum of biological potential at all the sites of occurrence.[12] In the past they were considered to be smooth muscle origin[13-17] but recent studies have shown a more complex picture with evidence of smooth muscle differentiation and neural differentiation (referred to as GANT, myentric plexus tumor).

GIST comprise a majority of tumors, previously diagnosed as GI leiomyomas ,leiomyoblastomas and leiomyosarcomas. It also includes many tumors previously considered as neurofibromas or schwannomas. Gastrointestinal autonomic nerve tumors is now understood as a variant of GIST by histology, KIT positivity and KIT mutation.[18] The exact incidence of GIST in the world is hard to determine, since the entity was not uniformly defined until the 1990's, when Rubin and colleagues used the SEER (surveillance, epidemiology and end results) cancer registry in US for patients with GIST from 1993-2002 to determine incidence. They found it to be 3.2/million.[19] In our 54 months study, 40 cases out of 48000 total GIT cases were GIST (0.12 %). The overall prevalence of GIST is higher because many patients survive for years with the disease.

GIST mainly affects the middle aged to elderly adults typically in their 60(s)[10,20] with no clear gender predilection. Some studies have demonstrated a slight male predominance.[21,22] GISTs are uncommonly seen in patients younger than 40 and rarely seen in second decade (<1%). In our study age ranged from 19-70 years though majority cases were of middle to elderly age. The mean age in our study is 45 years. 9 cases were having age less than 40 years and out of these, 3 cases were affected in the early twenties. In our study male to female ratio was 1:1, no sex predilection noted.

The majority of GIST are sporadic but GISTs have also been identified in association with neurofibromatosis type 1 (NF1); Carney traid syndrome characterised by a constellation of gastric GIST, extra adrenal paragangliomas and pulmonary chordoma; and Carney stratakis syndrome characterised by constellation of gastric GIST and paraganglioma.[7,23-30]

The majority of GIST (70%) present with non-specific clinical symptoms, which vary depending on the size and site of involvement. The symptoms can include bleeding, perforation and less commonly, obstruction.[10,11] Approximately 20% of cases were

asymptomatic. Overall metastases are uncommon and typically only seen in the setting of late stage disease with the exception of paediatric GIST which frequently present with lymph node metastases. Other metastatic sites include the liver, lung, bone, soft tissue or skin. According to literature found, Metastases are often seen more than 5 years after the initial surgery.[20,31,32] In our study, mostly patients presented with non-specific symptoms like abdominal pain, fatigue dyspepsia, nausea, anorexia, weight loss, fever. 2% of cases presented with threatening intra peritoneal haemorrhage and GI bleeding. 2/40 (5%) cases had lymph node metastases at the time of presentation and 1 case had metastases to liver.

More than 80% of GIST are primarily located in the GI tract and can involve any part of it with variable predeliction. Extra intestinal GIST are commonly found in soft tissues of omentum, mesentry and peritoneum.

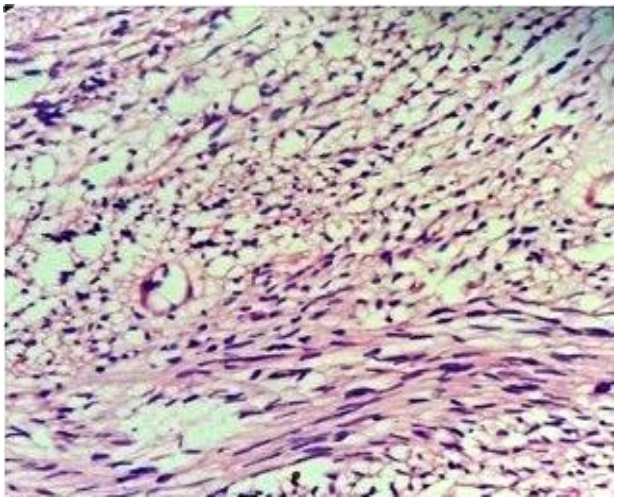

**Fig.6: Spindle Pattern of GIST (low and high power view).**

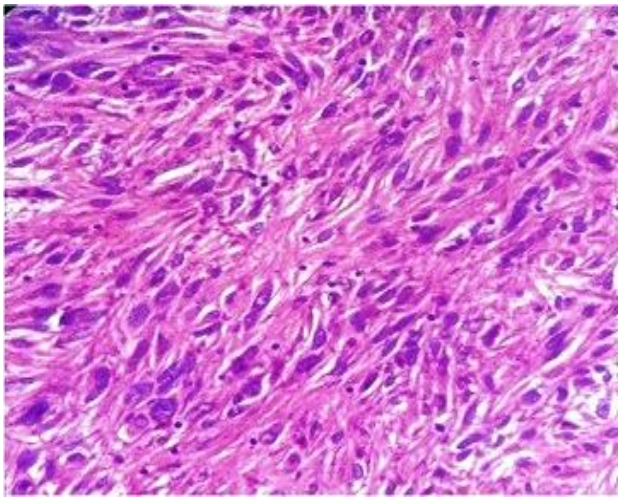

**Fig.7: Epitheloid Pattern of GIST (low and high power view).**

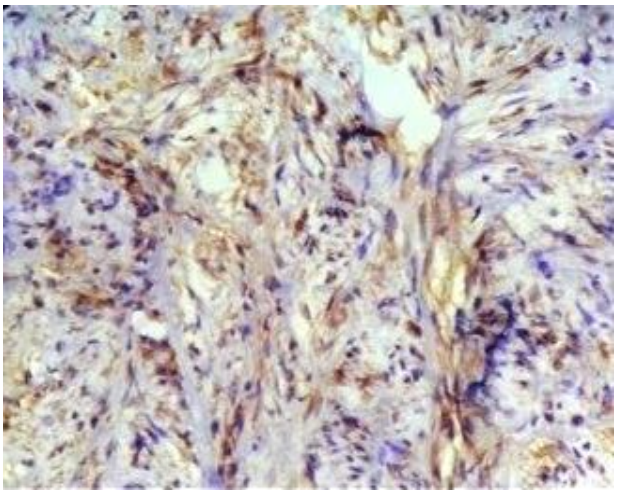

**Fig.8: CD117 positivity in GIST.**

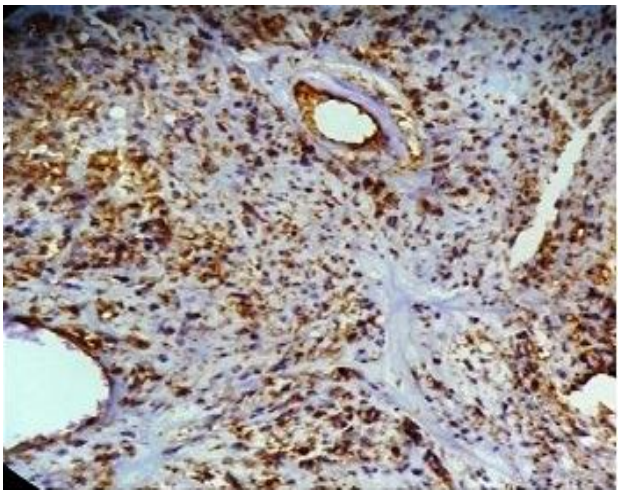

**Fig.9: CD 34 Positivity in GIST.**

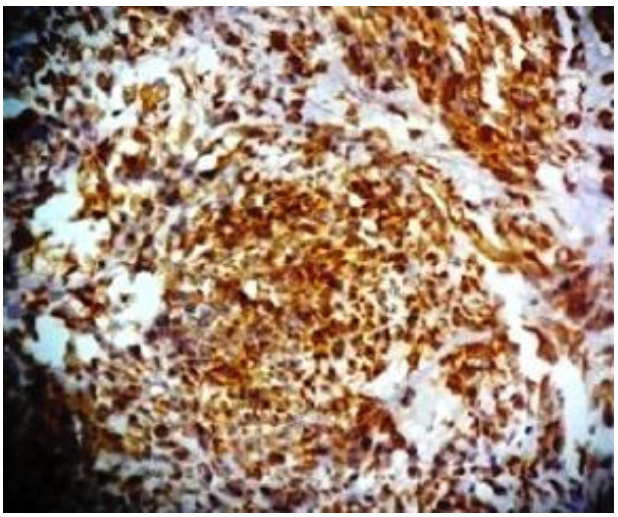

**Fig.10: Vimentine positivity in GIST.**

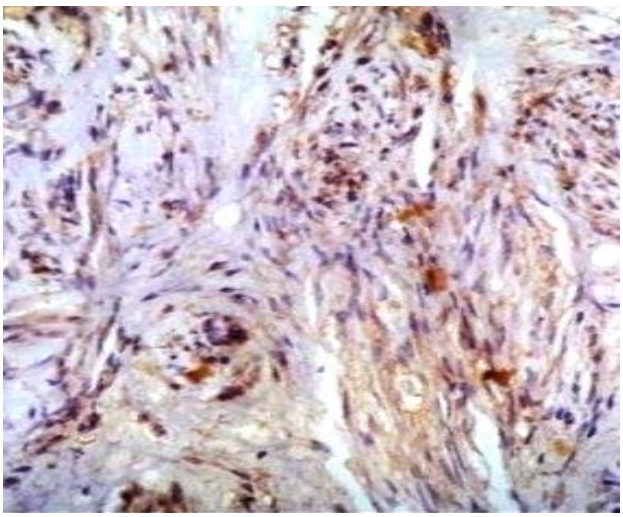

**Fig.11: DOG1 positivity in GIST.**

In most of the studies GIST commonly arise in the stomach (60%) followed by jejunum and ileum (30%), duodenum (5%), colorectum 4% and esophagus or appendix (1%).[33-39] In our study, most common site was small intestine (45%) followed by stomach (17.5%), mesentry (12.5%), retroperitoneum (7.5%), omentum (2.5), meckel's diverticulum (2.5%), colon(5%), liver(2.5%), pelvic fossa mass (2.5%) and upper chest wall (2.5%).

The tumor size in GIST is highly variable ranging from small mural nodules to large exophytic pedunculated mass. The average size is 7-8 cm. In our study, size ranged from 6 mm to 22 cm with the average size of 7 cm. Most of the cases were well circumscribed nodular or bosselated. Cut surface of tumor was grey to pink with rubbery or soft consistency. In some of the cases cut surface showed cystic degeneration and intramural haemorrhage. GIST is monotonous tumors that can be divided into three principal subtypes depending on the morphology. These include Epitheloid, Spindloid and mixed pattern. The majority of the GIST (approx of 70% of cases) were composed of spindle cells with pale eosinophillic fibrillary cytoplasm, ovoid nuclei and syncytial cell borders. Paranuclear vacuolization is frequently seen. Extracellular deposits of dense, collagen (skenoid fibres) are also seen. The cells are arranged in short fasciles or whorls (Fig.6). About 20% of cases are composed of epitheloid cells with pale eosinophillic to clear cytoplasm and round nuclei.The cells are arranged in nests, sheets and less commonly in cords (Fig.7).This morphology is commonly seen in paediatric GIST.[27,40] The remaining 10% of GIST have a mixed spindle and epitheloid cell morphology. In our study, 25/40 cases has spindle cell pattern (62.5); 9/40 cases had epitheloid configuration (22.5%) and remaining had mixed pattern (1.5%). After review of the literature & up to the best of our knowledge, no comparable figures found in other studies.

KIT expression is specific and sensitive marker for GIST with most of the cases showing a strong and diffuse cytoplasmic staining (Fig.8). A minority of cases can also exhibit a dot like or membranous staining pattern. The extent and pattern of KIT immunoreactivity has no impact on the likelihood of treatment response. In 60-70 percent of patients IHC for CD34 is also positive (Fig.9). Vimentin and SMA is positive in 15% to 60% cases (Fig.10).[35] In 10-15% of GIST, no detectable KIT or PDGFRA mutataion are seen. These are wild type GIST. Thus absence of mutations does not exclude the diagnosis of GIST. DOG1 is a calcium dependent, receptor activated chloride channel protein expressed in GIST. This expression is independent of type of mutation so it can be used for the diagnosis of KIT negative tumors.

In our study, 90% cases show positivity for CD117 and 10% cases were negative for CD117 but these are DOG1 positive (Fig.11).

## CONCLUSION

GISTs are the tumors with variable malignant potential, clinical course is well correlated with Predictive Prognostic factors. Hence close follow up of patients is advised to check for drug resistance or sign of recurrence.

More population based studies are needed to know the exact incidence and causative factors responsible for new mutations. Present study attempts to summarize the current knowledge and recent advances regarding the histogenesis, pathology, clinical picture, investigation and IHC findings which are the basis for novel targeted cancer therapy and evidence based management (surgical /non-surgical) of these unique tumor. The limitations of our study in absence of molecular findings which if present are very beneficial for patient prognosis.

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