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Histomorphological And Immunohistochemical Evaluation of Spindle Cell Neoplasm of Gastrointestinal Tract At Tertiary Care Centre

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Abstract

Introduction- Spindle cell neoplasms within the gastrointestinal tract (GIT) are less frequently encountered compared to epithelial tumors. GIST is the most frequent mesenchymal tumor of the alimentary canal accounting for 80% of cases . It can be classified as extra-gastrointestinal GIST, which originate in the omentum, mesentery, or retroperitoneum or as gastrointestinal. The most common location in GI site is the stomach, which accounts for 60% , followed by jejunum and ileum approximately 30%[6], duodenum 5% , and colon and rectum 5%.Despite the small percentage of mesenchymal tumor specifically with spindle cell morphology in GI tract, the striking overlap in the histomorphology of these tumors poses great diagnostic challenges and necessitates the use of an additional panel of immunohistochemical antibodies for characterization of specific entity. The differentiation based on detection of specific immunohistochemical markers improves the diagnostic accuracy and consequently facilitates the application of most appropriate therapeutic approach.

Aims & Objective- To study the histomorphological diversity of spindle cell neoplasm of gastrointestinal tract , to assess the prevalence of spindle cell neoplasm of gastrointestinal tract and to outline significance of various immunohistochemical markers for categorization of spindle cell neoplasm

Methods & material- The present study is a prospective observational study and cases were taken from Gastro-surgery department of IGIMS, Patna. In present study all cases of gastrointestinal tract tumor admitted and undergone surgical procedures during the study period were taken. A total of 38 cases were studied during the study period from October 2022 to June 2024. All samples received during the study period were grossed for histomorphological examination followed by immunohistochemistry.

Results- The age range included in our study was from 10 to 79 years. The most common age group was 40-49 years and least common age group had bimodal presentation from 10 to 29 and from 60 to 79 years. Majority (32 case, 84%) of tumor of GIT were spindle type. Less common (6 cases, 16%) were of mixed (spindle+ epitheloid) type. 36 of the primary tumors (95%) were unifocal while only 2 tumors(5%) found to be multifocal in nature.

Conclusion- GIST needs to be distinguished from other mesenchymal tumors. Clinical, histomorphological along with Immunohistochemistry [IHC] enables definitive diagnosis. DOG1 is useful in diagnosis of C-kit negative GIST. Risk stratification considering the anatomical location, size and mitosis prompts optimum management and targeted therapy.

INTRODUCTION

Spindle cell neoplasms within the gastrointestinal tract (GIT) are less frequently encountered compared to epithelial tumors. These neoplasms form a heterogeneous group encompassing malignant, intermediate and benign entities with 100 fold higher incidence of benign spindle cell neoplasm. Although mesenchymal neoplasm of Gastrointestinal tract is rare, however, it frequently involves GIT more than any other visceral organs with global incidence of 30-50 cases per million person-year [1,2]. These lesions originate from mesenchymal tissues and may stem from fibroblasts, smooth muscles, neural tissue, or endothelial cells[3]. As a general approach to GIT mesenchymal tumors, the precise anatomical location within digestive tract with characteristic origin from the various components of GIT wall is crucial for establishing a preliminary differential diagnosis. A general overview of the favored anatomic location within digestive tract includes

mucosa, submucosa and muscularis propria. Lesions common in mucosa are benign epithelioid nerve sheath tumors, sporadic ganglioneuroma, Schwann cell hamartoma, psammomatous melanotic schwannoma, benign fibroblastic polyp, perineuroma, leiomyoma and Kaposi sarcoma. Submucosal lesions include inflammatory fibroid polyps and lipomas. Lesions present in muscularis propria are gastrointestinal stromal tumor (GIST), leiomyoma, leiomyosarcoma, inflammatory myofibroblastic tumor, fibromatosis, schwannoma, GI clear cell sarcoma and plexiform fibromyxoma [4]. It has been found that this general approach is helpful to a large extent, but there can be exceptions and overlap between layers. Furthermore, it is imperative to prioritize the identification of gastrointestinal stromal tumor (GIST) among all spindle cell neoplasms as GISTs are considered to be a potentially malignant tumor and feasible potential targeted chemotherapy in the form of tyrosine kinase inhibitors (imatinib).

GIST is the most frequent mesenchymal tumor of the alimentary canal accounting for 80% of cases [5] . It can be classified as extra-gastrointestinal GIST, which originate in the omentum, mesentery, or retroperitoneum or as gastrointestinal. The most common location in GI site is the stomach, which accounts for 60% [7,8], followed by jejunum and ileum approximately 30%[6], duodenum 5% [9], and colon and rectum 5% [8]. Minority of cases occur in esophagus, appendix, gallbladder, mesentery, omentum. GISTs are thought to originate from interstitial cells of Cajal (ICCs) [10,11]. GISTs frequently exhibit constitutively activating mutations in the KIT gene, while approximately 5% constitutively activating mutation in PDGFRA [12]. No KIT or PDGFRA mutation is present in 10–15% of GISTs. Mostly these tumors are sporadic yet some of them are associated with syndromes like succinate dehydrogenase (SDH) complex deficiencies, neurofibromatosis type 1 (NF1), Carney stratakis syndrome and PDGFRA activating germline mutations [13]. Majority of GISTs showed positivity CD117 immunohistochemistry due to prevalent activating c-kit mutations [14].

Other than GISTs, leiomyoma and schwannomas are the next main mesenchymal tumors of GIT with spindle cell morphology which needs to be differentially diagnosed based on morphology and immunohistochemistry [15]. Leiomyoma, a benign pure smooth muscle tumor located primarily in distal oesophagus, colon and rectum and rarely in the stomach and small intestine. Schwannoma is a benign spindle cells neoplasm accounting for approximately 3% of all GI mesenchymal tumors located predominantly in the stomach and only rarely in esophagus, colon, and rectum. [1,2]. The less common group of mesenchymal neoplasm exhibiting spindle cell morphology includes desmoid tumor, inflammatory fibroid polyp, inflammatory myofibroblastic tumor, solitary fibrous tumor, leiomyosarcoma etc.

Despite the small percentage of mesenchymal tumor specifically with spindle cell morphology in GI tract, the striking overlap in the histomorphology of these tumors poses great diagnostic challenges and necessitates the use of an additional panel of immunohistochemical antibodies for characterization of specific entity. The differentiation based on detection of specific immunohistochemical markers improves the diagnostic accuracy and consequently facilitates the application of most appropriate therapeutic approach.

AIMS AND OBJECTIVES

1) To study the histomorphological diversity of spindle cell neoplasm of gastrointestinal tract.
2) To assess the prevalence of spindle cell neoplasm of gastrointestinal tract.
3) To outline significance of various immunohistochemical markers for categorization of spindle cell neoplasm.

TUMOR MARKERS

The antibodies used in immunohistochemical markers for differential diagnosis of spindle cell neoplastic tumor of GIT include c-Kit, DOG1, Desmin, S100, α-smooth muscle actin (α-SMA), CD34, and Ki-67. Ki-67 is important for predicting tumor recurrence.

C-KIT/CD117

CD117, also known as c-kit, is a receptor tyrosine kinase that is crucial for the development and proliferation of various cell types, including erythroblasts, germ cells, melanocytes, mast cells, and interstitial cells of Cajal (ICCs). Its activity is triggered by binding to its ligand, stem cell factor (SCF), which activates signaling pathways essential for cell survival, proliferation, and differentiation. Abnormalities in the c-kit gene or its expression can lead to various disorders, including certain types of cancers and mast cell diseases. Immunohistochemical analysis has shown that 95% of gastrointestinal stromal tumors (GISTs) are strongly and diffusely positive for KIT (CD117). In GISTs, KIT expression can present with membranous, cytoplasmic, or paranuclear staining patterns [21].

DOG-1

Discovered on GIST1 **(**DOG1**)** gene is a transmembrane calcium-activated chloride channel protein. DOG-1 is an emerging marker that has shown promise in early studies as a more sensitive and specific marker than c- KIT especially in a subset of KIT-negative GISTs. KIT and DOG1 show very similar expression pattern. However, DOG1 may be more clearly positive in some PDGFRA mutant GISTs [22].

CD-34
CD34 is predominantly used as a marker for hematopoietic progenitor and stem cells. This glycoprotein is found on cells that are involved in cell-cell adhesion. About half of gastrointestinal stromal tumors (GISTs) outside the stomach are CD34 negative, while over 90% of gastric GISTs are CD34 positive [23]. CD34 stains nearly 100% of solitary fibrous tumors and does not typically stain Leiomyomas or Fibromatoses [24].

S-1OO
The calcium-binding S100 protein family is commonly found in melanocytes, Schwann cells, chondrocytes, myoepithelial cells, and other cell types. S100 protein is consistently positive in all schwannomas but negative in all gastrointestinal stromal tumors (GISTs) and smooth muscle cell tumors [24].

ALFA- SMA
Smooth muscle actin (SMA) is one of the six actin isoforms which constitutes a significant part of the cytoskeletal structural network in smooth muscle cells, myofibroblasts, and myoepithelial cells. SMA is present in all benign and malignant smooth muscle tumors, the majority of glomus tumors, inflammatory myofibroblastic tumors, and inflammatory fibroid polyps. However, a substantial portion of gastrointestinal stromal tumors (GISTs), especially those in the small intestine (up to 47%) and 10- 13 % of rectal and esophageal GISTs, also test positive for SMA [24].

DESMIN
Desmin is a 53-kDa intermediate filament protein that is characteristically found in cardiac, smooth, and striated muscle cells. The clones D33, DER-11, and DEB-5 are the 3 most used monoclonal antibodies to desmin[25] Therefore, Leiomyomas are strongly positive for desmin, whereas leiomyosarcomas show variable positive staining for desmin, which may be partial, weak, or negative. On the contrary, neurogenic tumors and GISTs are negative for desmin [24].

Ki- 67
Ki-67 is a widely recognized marker of cell proliferation, detectable during all active phases of the cell cycle (G1, S, G2, and M) but absent in resting cells. It is useful for predicting tumor recurrence, as a high Ki-67 labeling index typically correlates with a greater risk of recurrence. In gastrointestinal stromal tumors (GISTs), Ki-67 is a dependable marker for both prognosis and recurrence prediction [24]. Liang et al. found that GIST patients with a Ki-67 index < 5% had higher death free survival while high Ki- 67 index >10% was an independent predictor of poor overall survival [26].

Beta-Catenin β-Catenin plays a crucial role in the Wnt and E-cadherin signaling pathways, both of which are significant in tumorigenesis. The presence of nuclear β-catenin can be detected using immunohistochemistry. In addition to desmoidtype fibromatoses, up to 24% of solitary fibrous tumors show positive staining for Beta-catenin. However, solitary fibrous tumors and desmoid type fibromatoses are morphologically distinct.[24]

PROCEDURE:
The studies were conducted on the surgical specimens which were received in department of Pathology

RESULT & INTERPRETATION
The present study is a prospective observational study and cases were taken from Gastro-surgery department of IGIMS, Patna. In present study all cases of gastrointestinal tract tumor admitted and undergone surgical procedures during the study period were taken. A total of 38 cases were studied during the study period from October 2022 to June 2024. All samples received during the study period were grossed for histomorphological examination followed by immunohistochemistry.

TABLE 1: AGE DISTRIBUTION OF GIT TUMOR

AGE GROUP	NO. OF PATIENTS (n=38)	PERCENTAGE %
10 – 19 YRS	3	7.8
20 – 29 YRS	3	7.8
30 – 39 YRS	4	10.5
40 – 49 YRS	14	36.8
50 – 59 YRS	8	21.0
60 – 69 YRS	3	7.8
70 – 79 YRS	3	7.8

The age range included in our study was from 10 to 79 years. The most common age group was 40- 49 years and least common age group had bimodal presentation from 10 to 29 and from 60 to 79 years.

GRAPH: AGE DISTRIBUTION OF GIT TUMOR

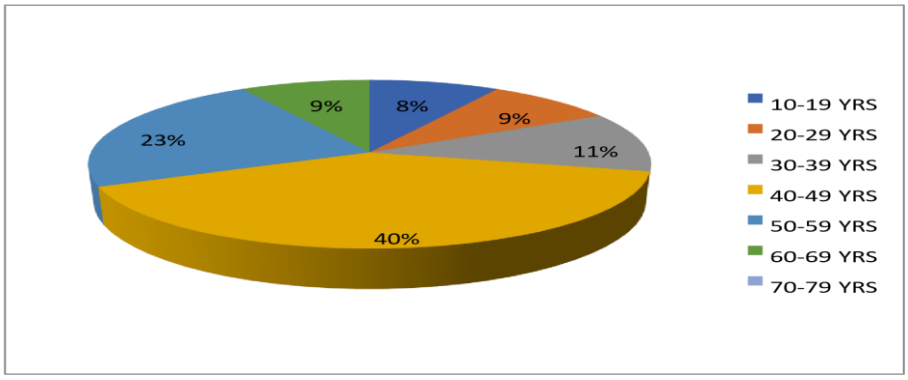


TABLE 2: SEX DISTRIBUTION OF GIT TUMOR

SEX	NO. OF PATIENTS (n=38)
MALE	22
FEMALE	16

Majority of the patients were male comprising 58% (22) with only 16 females (42%) in the study group.

GRAPH: SEX DISTRIBUTION

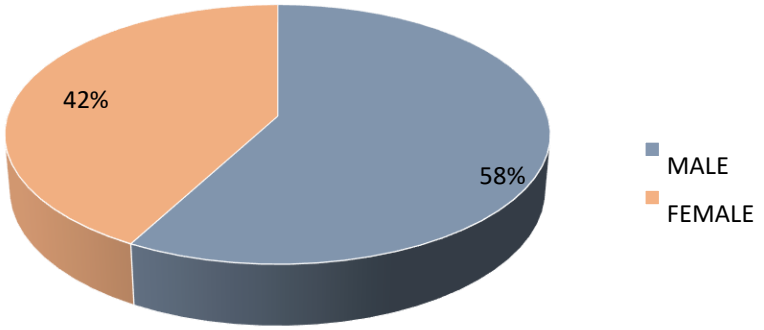


TABLE 3: SITE OF PRIMARY GIT TUMOR

SITE OF TUMOR	NO. OF PATIENTS (n=38)	PERCENTAGE %
ESOPHAGUS	1	2.6
STOMACH	22	57.8
SMALL INTESTINE	12	31.5
LARGE INTESTINE	1	2.6
EXTRAPERITONEAL	2	5.2

22 patients (57.8%) had primary disease in stomach. 12 patients (31.5%) presented with small intestinal tumor. 2 patients had extra peritoneal mass including mesentery mass. One patient each had primary tumor localized to the esophagus and large intestine.

GRAPH: SITE OF TUMOR

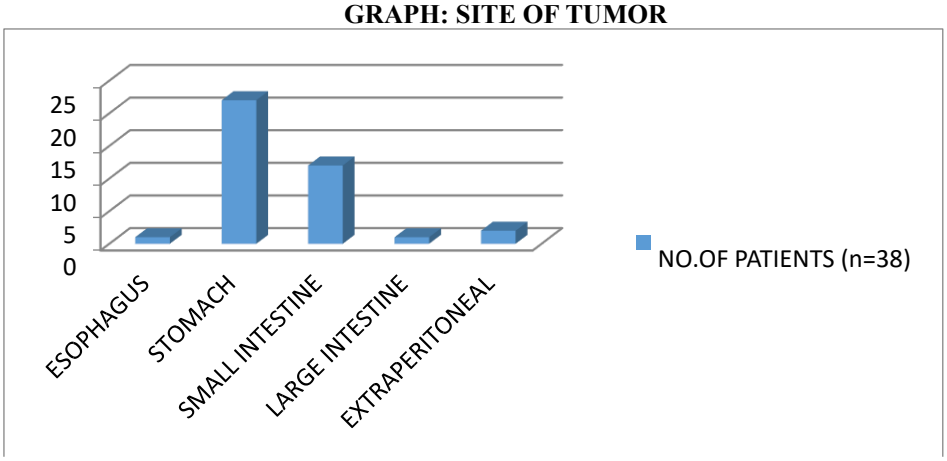


TABLE 4: CLINICAL PRESENTATION OF GIT TUMOR

CLINICAL FEATURES	FREQUENCY	Percentage %
PAIN ABDOMEN	14	36.84
ANEMIA	28	73.68
ABDOMINAL MASS	4	10.52
MELENA	15	39.47
PERFORATION	3	7.89
OBSTRUCTION/ INTUSSCEPTION	1	2.63

Anemia was the predominant symptom, seen in 28 patients constituting 73.68%. Second most common presenting symptom was GI tract bleeding (hematemesis/melena) in 15 patients. 14 patients presented with pain abdomen. 4 patients presented with abdominal mass. Of the 3 patients presenting as acute emergency, 1 had features of intestinal obstruction, while 3 presented with perforation and peritonitis.

GRAPH: CLINICAL PRESENTATION

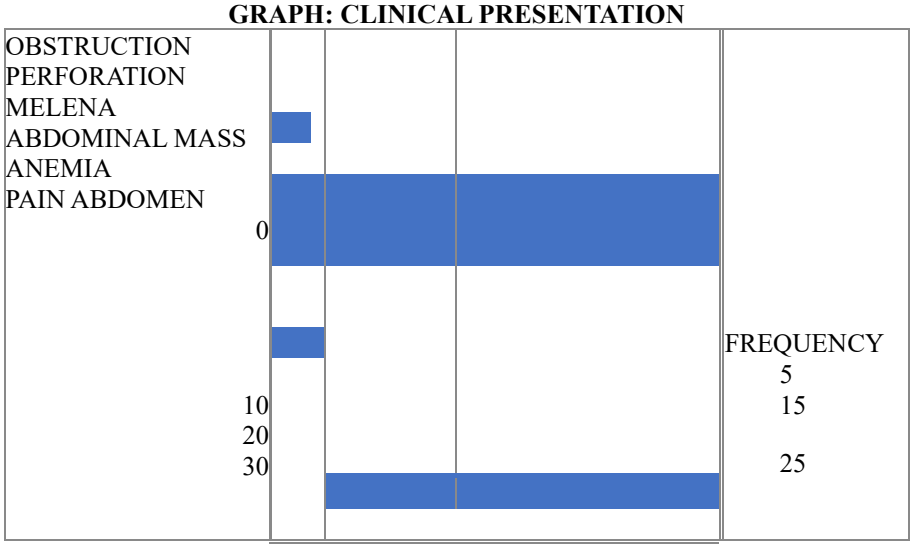


TABLE 5: GROSS FEATURES IN PRIMARY GIT TUMOR

GROSS	FREQUENCY (n=38)	PERCENTAGE %
SUBMUCOSAL&INTRAMURAL	18	47.36
SEROSAL	4	10.52
NECROSIS	6	15.78
MULTIPLE	2	5.26
MESENTRY/OMENTAL	3	7.89
HEMORRHAGE	1	2.63
CYSTIC CHANGE	4	10.52

18 specimens (47.36%) on grossing had sub mucosal and intramural location. 4 specimen(10.52%) had serosal tumor . 6 solid tumors(15.78) had necrotic area and 4 specimens(10.52%) were found to have solid tumor with cystic area. 3 specimen(7.89%) had tumor attached in mesentery/ omentum. 2 specimen(5.26%) had multiple nodular tumor and 1 had hemorrhagic area seen.

GRAPH: GROSS FEATURE

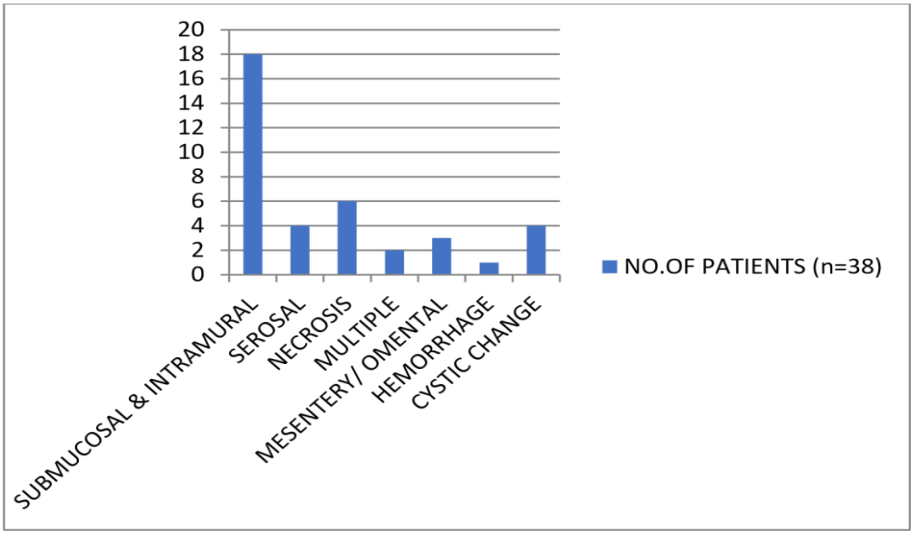


TABLE 6: HPE TYPES OF GIT TUMOR

HPE TYPES	FREQUENCY	PERCENTAGE %
SPINDLE	32	84
MIXED	6	16
TOTAL	38	

Majority (32 case, 84%) of tumor of GIT were spindle type. Less common (6 cases, 16%) were of mixed (spindle+ epitheloid) type.

GRAPH: HPE TYPES OF GIT TUMOR

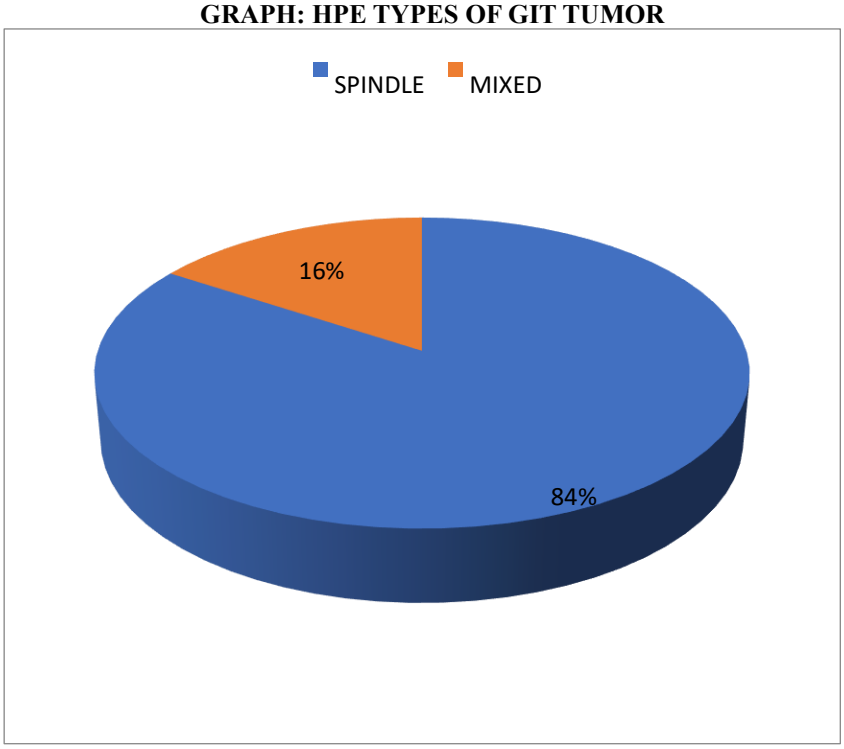


TABLE 7: FOCALITY OF PRIMARY GIT TUMOR

FOCALITY	FREQUENCY
UNIFOCAL	36
MULTIFOCAL	2

36 of the primary tumors (95%) were unifocal while only 2 tumors (5%) found to be multifocal in nature.

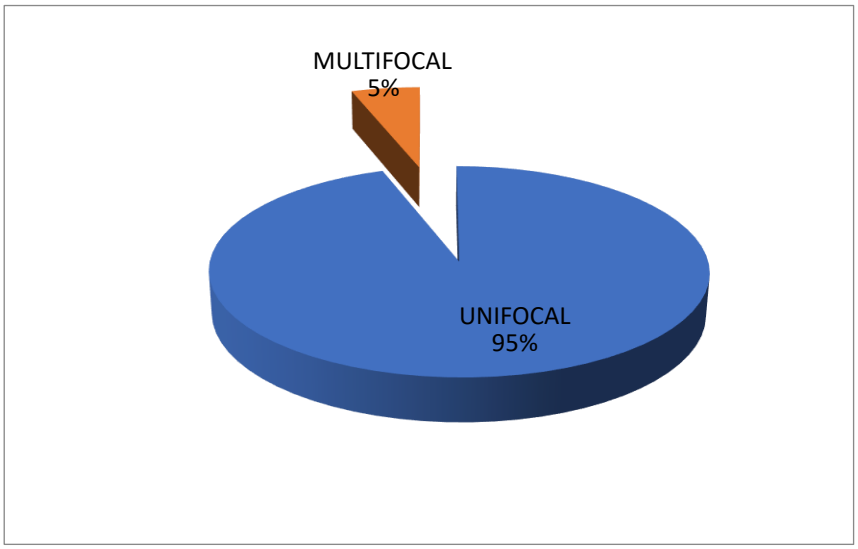


TABLE 8: SIZE OF PRIMARY GIT TUMOR

SIZE (cm)	NO. OF PATIENTS (n=38)
≤2	1
>2 to ≤5	15
>5 to ≤10	13
>10	9

The majority of patients (15) had primary tumor size in the range from>2to ≤5cm, 13 patients between 6 to 10 cm, while 9 patients had > 10cm in size. One patient had primary tumor size <2 cm. The tumors studied showed wide variation in size, with the smallest measuring 1.5cm and the largest measuring 18cm.

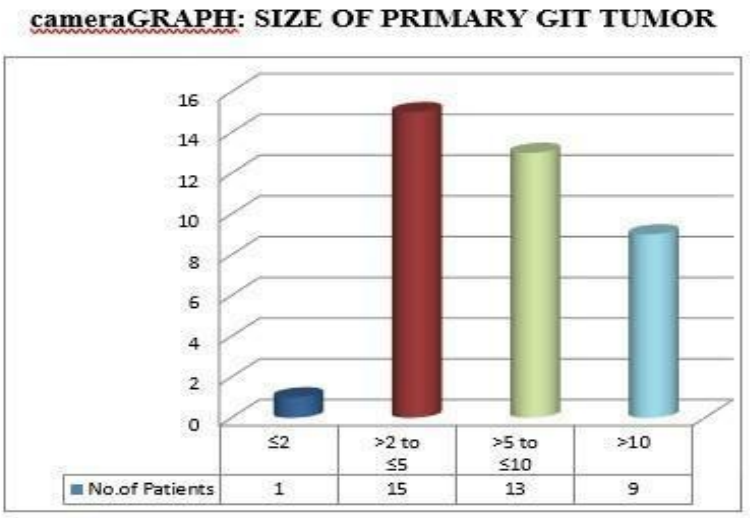


TABLE 9: DISTRIBUTION OF GIT TUMOR AS PER MITOTIC RATE.

Mitotic index	No. of patient (n=38)
≤5 / 5mm^2	30
>5 / 5mm^2	8

Most (79%) of the tumor had favorable mitotic rate (≤5/5mm^2). Eight of tumor (21%) had unfavorable mitotic rate (>5/5mm^2).

GRAPH: MITOTIC RATE

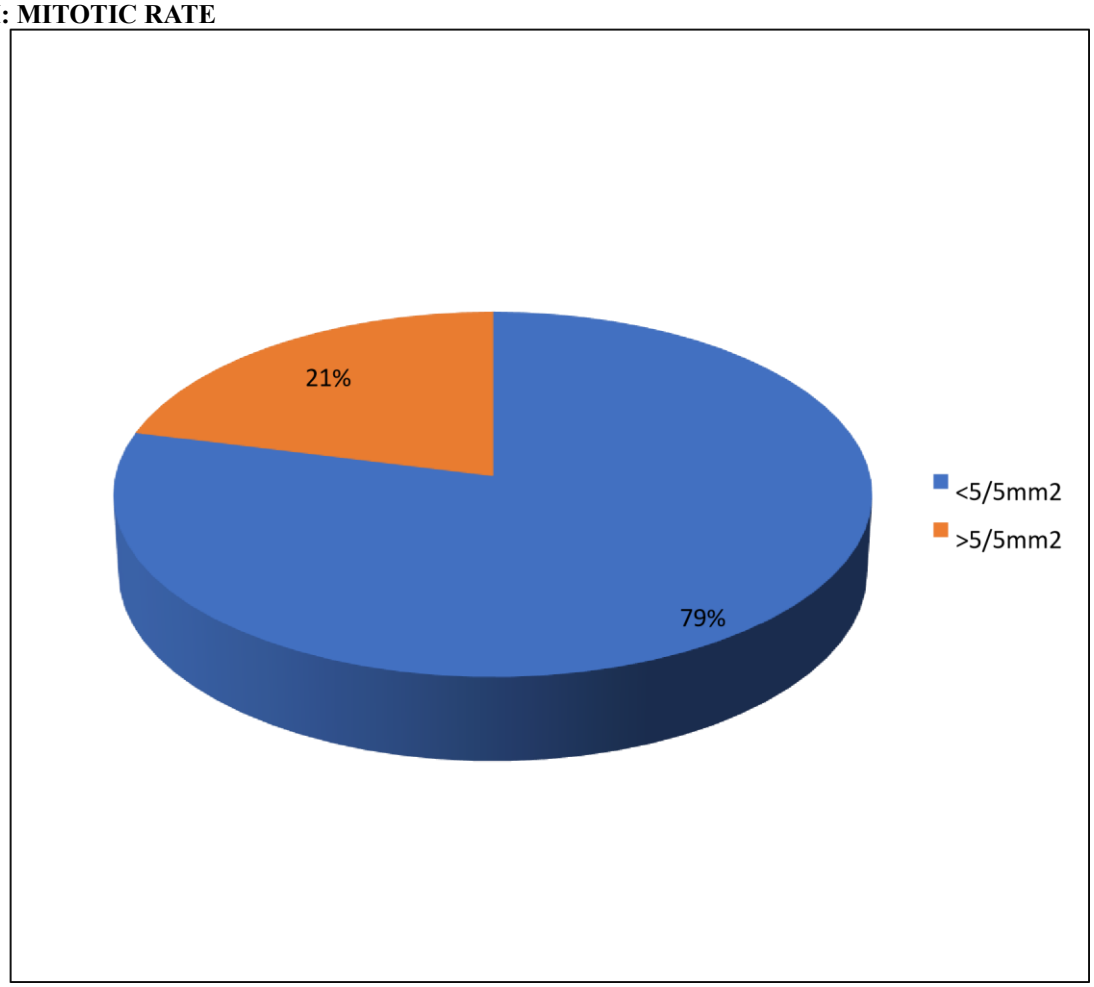


TABLE 10: DISTRIBUTION OF PRIMARY GIT TUMOR AS PER NECROSIS.

NECROSIS	FREQUENCY	PERCENTAGE
PRESENT	6	15.7
ABSENT	32	84.2

Most (84%) of the tumor had no necrosis, while six (16%) tumor was found to have necrotic area.

FLOWCHART: DIFFRENTIAL DIAGNOSIS OF SPINDLE CELL TUMOR OF GIT

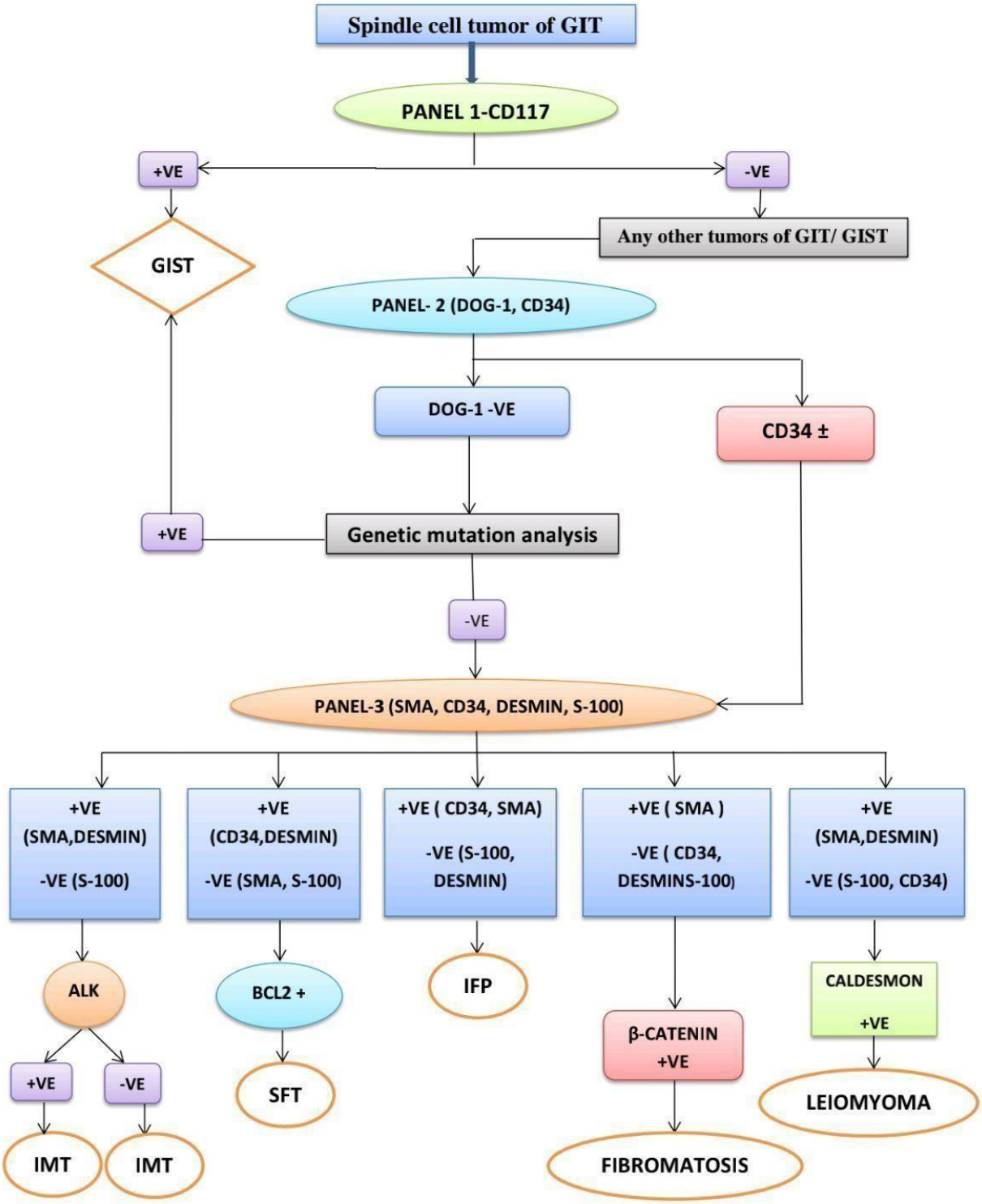


TABLE 11: CONFIRMATION OF HPE BY IHC.

Tumor	Immunohistochemistry						
	CD117	DOG-1	CD34	SMA	DESMIN	S-100	Others
GIST	+	+	+	±	-	-	
IMT	-	-	-	+	+	-	ALK(+)
SFT	-	-	+	-	+	-	BCL-2(+)
FIBROMATOSIS	-	-	-	±	-	-	β-catenin (+)
LEIOMYOMA	-	-	-	+	+	-	h-Caldesmon(+))
IFP	-	-	+	+	-	-	

TABLE 12: CLASSIFICATION OF GIT TUMOR AFTER IHC APPLICATION

TUMOR	NO. OF PATIENT (n=38)	PERCENTAGE %
GIST	28	73.6
IMT	5	13.1
SFT	2	5.2
FIBROMATOSIS	1	2.6
LEIOMYOMA	1	2.6
IFP	1	2.6

An attempt has been made to study the histomorphological spectrum of spindle cell tumor following the above mentioned flow chart with application of our IHC panel (comprised of CD117, DOG1, CD34, SMA, DESMIN and S-100) along with others (ALK, BCL-2, Beta-catenin and h-caldesmon) which had been applied separately. Out of 38 cases , 28 cases (73.6%) were diagnosed as GIST tumor, while 5(13.1%) cases of Inflammatory myofibroblast tumor (IMT). 2 cases of tumor diagnosed as solitary fibrous tumor(SFT) and 1 each case of fibromatosis, leiomyoma and Inflammatory fibroid polyp(IFP) as final diagnosis.

GRAPH: HPE DIAGNOSIS OF TUMOR

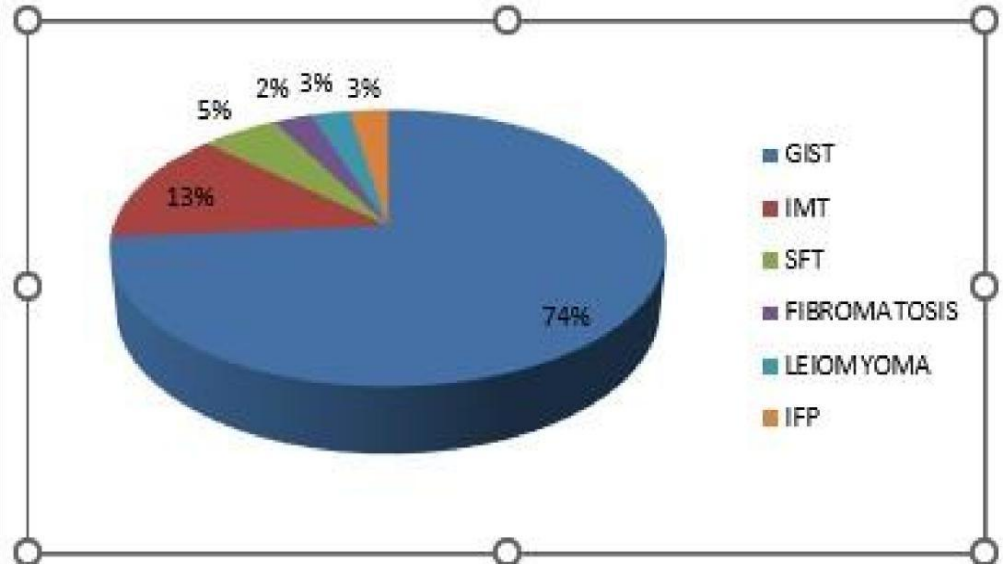
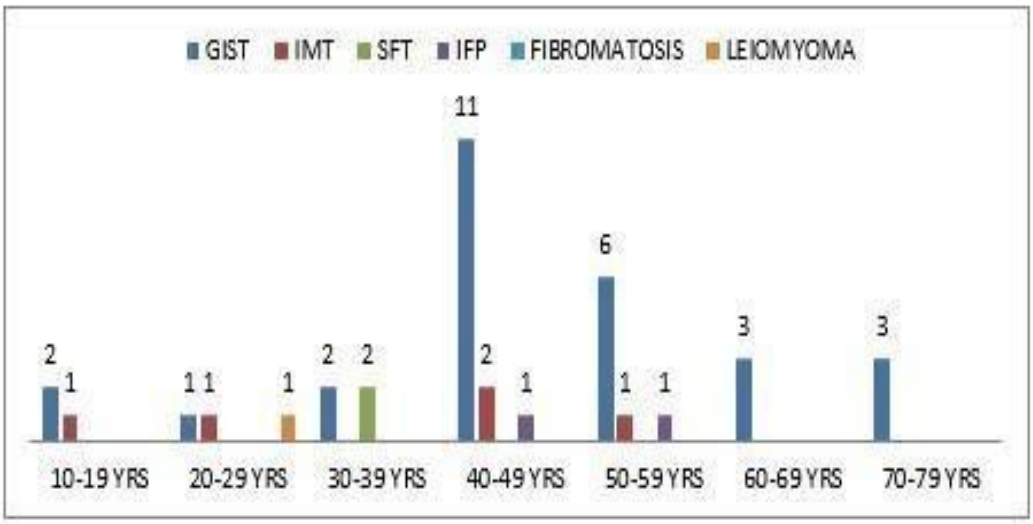


TABLE 13: AGE DISTRIBUTION OF TUMOR AFTER HPE DIAGNOSIS

AGE RANGE	GIST	IMT	SFT	IFP	FIBROMATOSIS	LEIOMYOMA	TOTAL	AVERAGE	%
10-19	2	1					3	3	7.89
20-29	1	1				1	3	3	7.89
30-39	2		2				4	4	10.52
40-49	11	2			1		14	14	36.84
50-59	6	1		1			8	8	21.05
60-69	3						3	3	7.89
70-79	3						3	3	7.89
TOTAL	28	5	2	1	1	1	38	38	100

GRAPH: AGE DISTRIBUTION OF TUMOR AFTER HPE DIAGNOSIS



In our study the patients presenting with complain of GIT tumor having spindle cell neoplasm presented in a wide range of age group from 12 years to 72 year old . Most common type of tumor of GIT was GIST comprising 73.6% were found predominantly in age group of 40-49 years.

DISCUSSION

In GIT, epithelial neoplasm ranging from benign to malignant outnumbers the mesenchymal neoplasm. Mesenchymal tumors of the gastrointestinal tract (GIT) are heterogeneous group of tumor with wide range of clinical presentation. It may be detected incidentally on endoscopy to a resection of highly malignant sarcoma. GISTs should always be considered in the differential diagnosis of spindle cell tumors of the GIT, as GISTs constitute the largest subset of mesenchymal tumors of the GIT and the most common sarcoma.[1] If the incidence of spindle-cell tumors in the gastrointestinal tract is corrected for the normal decay of population, it will be seen that there is a consistent rise in their appearance with age. There is no relative increase in the malignant varieties with increasing years.

In present study, 38 patients were analyzed for spindle cell neoplasm of gastrointestinal tract. It comprises 22 men (58%) and 16 women (42%) with a male – female ratio 1.37:1. Rasool Z et al did their study in Kashmir valley in 2019 on histomorphological spectrum of spindle cell tumor and found male female ratio of 2.3:1[3]. Majority of the study were done on mesenchymal neoplasm of GI tract or on GIST. In present study, total patients with GIST were 28 with male female ratio of 1.8:1. Similar study done by Satwik N et al. on Gastrointestinal stromal tumors found male female ratio of 2:1 in North India [52] which is near similar to our study.

Ages of the patients ranged from 12 to 72 years, mean age of 46 years. Maximum cases were seen in the age range of 4049 age range constituting 14 cases (36.84%). It was also found that the maximum (73.68%) patients were above 40 years of age. Rasool Z et al. found patients in age range of 38-75 years and predominant age group was >50 years [3]. There was a spectrum of median age incidence outlined in various studies conducted in different parts of the world for gastrointestinal neoplasm. In the western world, it was 71 years in the USA which was less in Asian countries, like in Japan it was 61 years, in Pakistan 48 +/- 4.47 years , in Saudi Arabia 47 years. In present study, the median age was 46 years which is near similar to the study done in Pakistan and in India by Lamba M et al. with mean age of presentation 48.2 years[58]. Baa AK et al. [49] and Satwik N et al. [52] found slight high median age 53 years and 55 years respectively. A study done by Jandial A et al. in year 2022 on GIST in Jammu region, India found mean age of 53.55 years [13].

In present study, most common location was the stomach in 22 patients (57.8%), followed by the small intestine (jejunum and ileum), extra- peritoneum, large intestine, and esophagus. Similar observation was made by Rasool Z et al[3] . They also found maximum cases in stomach followed by small and large intestine. A study based on the Surveillance, Epidemiology and End Results (SEER) registry data from the USA on GIST, found 51% cases from stomach, 36% from the small intestine, 7% from the colon, 5% from the rectum, and 1% from the oesophagus [60].

In present study, 75% of cases of GIST arose from stomach, 4% jejunum and 21% from ileum. Jandial A et al. found

GIST in stomach in 30 cases (66.7%), followed by the small intestine, colon and rectum [13] . Baa AK et al. Included 120 patients with GIST who found most common site of the primary was the stomach (50%), followed by the small intestine (37%) [49].

The most common presentation in our study was anemia in 28 patients (73.68%), gastrointestinal bleeding in 15 patients (39.7%), followed by abdominal pain in 14 patients (36.84%), abdominal mass in 4 patients (10.52%), gastrointestinal perforation in 3 patients (7.89%), intussusception in 1 patients (2.63%) which was in sharp contrast with Rasool Z et al who found pain in abdomen in all the 30 patients. Our findings of anemia and GI bleeding were concordant with study done by Miettinen M et al. on Gastrointestinal Stromal Tumors. They also found that the most common presentation of GIST is anemia and GI bleeding. This may be acute (melena or hematemesis) or chronic insidious bleeding leading to anemia .Our study correlate with study done by Miettinen M et al.[60].
In present study 18 specimens (47.36%) had tumor in sub-mucosal and intramural location. 4 specimen (10.52%) had serosal tumor . 6 solid tumors(15.78) had necrotic area and 4 specimens(10.52%) were found to have solid tumor with cystic area. 3 specimen(7.89%) had tumor attached in mesentery/ omentum. 2 specimen(5.26%) had multiple nodular tumor and 1 had foci of hemorrhage.
A study done by Ravikumar G et al. on Clinicopathologic spectrum of gastro intestinal stromal tumours found that Intramural & submucosal tumor were 10/20 (50%) which is concordant with present study[62].
In this study, the cellular morphology of GISTs were predominantly spindle shaped (78.57%) and less commonly mixed type (21.43%) which was similar with the observation made by Jandial A et al and Jumniensuk C et al. who found 70% and 75% respectively of GIST showing spindle cell morphology. In this study most of the tumors were unifocal (36 cases, 95%) while multifocal was found in 2 cases (5%).
A study done by Jumniensuk C et al. on 76 cases of GIST found most of the tumors were unifocal (70 cases, 92.1%) while multifocal were found in 4 cases (5.3%) which correlate to our study.

On IHC examination, out of all 38 cases of spindle cell tumor of GIT 28 cases (73.68%) were diagnosed GISTs and 10 cases non –GIST tumors. 26 cases of GISTs were positive for CD117 (92.85%), only 2 cases (5.26%) were CD117 negative, which was positive for DOG1. 18 cases of CD117 positive cases were also positive for DOG1. In 9 cases of CD117 positive case DOG1 was not done. Only 1 case of CD117 positive was found DOG1 negative. Other IHC markers positive in GIST were CD34 (42%), SMA (17%), desmin (5.26%), and S100 was negative in all 38 cases (100%). While among non- GIST cases, 5(13.1%) were of IMT which were positive for SMA and DESMIN. Two cases out of 5 case of IMT were further examined and found ALK positive. 2 suspicious cases of tumor diagnosed as SFT which showed negativity for CD34, SMA and DESMIN positive .On further IHC examination was confirmed as BCL-2 positive. 1 (2.6%) case of Fibromatosis (SMA +ve, CD34 +ve) was found Beta-catenin nuclear positivity, Leiomyoma (h-caldesmon+ve) and IFP(CD34 and SMA positive,) as final diagnosis.

Spectrum of spindle cell tumors in various studies in comparison to present study

Name of study	Total no. of cases	GIST	Smooth and skeletal muscle tumor	Adipose and myofibroblastic tumor	Neural tumor
Rasool Z et al. [3]	30	23 (76.7%)	2 (6.7%)	Fibromatosis-1, IMT-1 (6.7%)	2 (6.7%)
Jaypuriya A et al.[50]	92	39(90.7%)	8 (19.51%)	IFP-17.7% Fibromatosis8.69%	8(7.32%)
Vij et al. [62]	133	121(90.98%)	8 (6.01%)	2 (1.50%)	2 (1.50%)
Varsha et al[63]	39	32 (82.05%)	5 (13.00%)	1 (3.00%)	1 (3.00%)
Ogun et al. [64]	46	24 (52.17%)	9 (19.56%)	5 (10.87%)	none
Lakshmi et al.[65]	176	92 (52.30)	Others 17 (9.66%)		
Present study	38	28(73.68)	1(2.63%)	9 (23.68%). IMT-5(13.1%),IFP- 2.63%), Fibromatosis1(2.63%), SFT2(5.26%)	0

GIST remains the most frequent neoplasm amongst all spindle cell tumor including the present study. In present study , no single case of tumor of neural origin were found which was frequently found in above mentioned studies, which can be explained due to small sample size of the present study.

In this study, tumor sizes ranged from 1.5 to 18 cm with most of the tumors 39.47% were > 2to ≤5cm cm. In case of patients having GISTs tumors, most tumors 53% range from >2cm to 5cm. 25% were in range from 5 -10 cm and 18% were >10 cm. Ravikumar G et al. found 40% of cases with tumor size >10 cm. 30% were 5-10cm [61] . Similar study done by Jumniensuk C et al. found most(31 case 40.8%) of the tumor size were >5-10 cm [56]. Study done by Jandial A et al. found most (23cases,51.1%) of tumor were >5-10cm [13]. Our finding with respect to tumor were discordant with other authors .

In current study mitotic counts range from 0 to 11 per 5 mm^2 . Low mitotic counts (≤ 5/ $5mm^2$) found in 31 cases (82 %) and high mitotic counts (> 5/$5mm^2$) were observed in 7 cases (18%) . Tumor with GIST histomorphology showed mitotic rate ≤5/$5mm^2$ in majority (20 cases, 71%) and 8 cases (29%) with mitotic rate > 5/5 mm^2 · which was similar to study done by Satwik N et al. who found mitotic count <5/5 mm^2in 80% cases .[52]. Another study done by Jumniensuk C et al. found low mitotic counts (≤ 5/5mm2) in 55 cases (77.5%) and high mitotic counts (> 5/5mm2) in 16 cases (22.5%).

In this study proliferative index (Ki-67) ranged from 0-35%. In non-GIST tumor proliferative index ranged from 0% to <2% in benign tumors like leiomyoma, fibromatosis, IFP and SFT. In case of IMT it was varied from <1% to<3%.Whereas in GISTs tumors Ki-67 ranged from <1% to 35% among tumor having higher potential of malignancy. In this study out of total 38 spindle cell tumors, 6 cases (15.78%) showed necrosis. 3 cases of GIST with necrosis came under high risk category.

A study done by Ravikumar G et al. who found 10 out of 20 cases of GIST with necrosis of which 90% belonged to high risk category. This finding was not in accordance with our study on GIST.

In this study risk categorization based on size of tumor and mitotic rate revealed that most (17 cases, 60.71%) of tumors belonged to the low risk, while 1/3rd (10 cases, 35.71%) fell into the high risk category. All of the high risks GIST were from stomach origin. Only 2 cases comprising 5.26% were >10cm and mitosis >5/$5mm^2$ that metastasized to liver. There was no significant difference in the mean age of presentation in the various risk categories. Also there was no significant difference in the occurrence of high risk cases in men and women.

High mitotic counts per 5 mm2 were found correlated with metastasis similar to the report by Miettinen et al. [25] who found that mitotic activities are the most powerful prognosticators integrated with tumor size.

In present study, majority of the patients after surgical procedure were doing well on follow up. Some patients had minor complaints of dyspepsia post operatively. Out of total 38 cases of spindle cell neoplasm of GI tract, majority (95%) patients were alive. 2 patients of high risk category, who was lost for follow up presented with liver metastasis. They did not turn up for regular follow-up, did not receive any medication and visited to hospital when their condition deteriorated and succumbed to disease .

Patients with high risk potential were put on TKI inhibitor (Imatinib mesylate namely -Gleevec, STI-571)) drug therapy among which one patient came with recurrence .

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