Management of gastrointestinal stromal tumor in gastroenterology and hepatology teaching hospital

***Dr.Sajid Sabbar Whaib**
****Dr.Ahmed Hussein Magtouf**

ABSTRACT

Background: Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of the gastrointestinal (GI) tract.Variable malignant potential from low to highly aggressive. Different factors and immunohistochemical staining associated with the incidence of GISTA wide local resection with macroscopic and microscopic removal of the entire tumour is recommended.
Aim: To study the characteristics and expression of immunohistochemical staining and surgical options and outcomes of treatment of these tumors. **Patient and method:** This was a retrospective and prospective study included ,22 patients classified according to age ,sex, site and staging of the tumor at each organ, using of abdominal and endoscopic ultrasonographyCTscan and MRI,the percentage of each immunohistochemical staining expretion,morbidity and mortality associated with surgery and follow up, all patients received imatinib mesylate as adjuvant. **Results:**There were 13males and 9females, the main tumor site was stomach(63%) then small bowel(18%),colon(9%),rectum(4%), omentum(4%). High grade tumor in small and large bowel with relative low grad in the stomach.CD117was positive in(81%) and (59%)for CD34,and the surgical resection was the principal treatment. 3cases developed recurrence.
Conclusions: The immunohistochemical staining is the mainstay in the diagnoses of GIST, surgery is the only curative way in the management ,and the tyrosine kinase inhibitor offering hope for the patients.

Introduction:

Gastrointestinal stromal tumors (GISTs) are the most commenmesenchymal neoplasms of the gastrointestinal tract[1],located primarly in the GIT tract[2] ,it compromise 0.2% of all gastrointestinal tract(GIT) tumors and 80% of GIT mesenchymal neoplasms[3]. In the past,they were thought to start in muscle or nerve cells in the GI tract. This is because the tumour cells look like muscle or nerve cells under the microscope.[4]GISTs start in special cells found in the wall of the GI tract, called the*interstitial cells of Cajal*(ICCs), or in very early cells that can develop into ICCs. which are part of the autonomic nervous system[5].GISTs result from a mutation in one of the receptor protein tyrosine kinases(KIT,also called CD117)[6-8]Although *KIT* mutation is important, it is not sufficient by itself for malignant transformation in GISTs. In a minority of cases, GISTs result from mutational activation of the closely related tyrosine kinase PDGF receptor a (PDGFRA).[12,13]Evidence suggests that KIT and PDGFRA activation have similar biological ramifications,[12]which may be expected due to their structural similarities.

The annual incidence of GISTs varies worldwide, in USA is 6.8 cases/1000000,whereas in Finland it is 10-20/million/year for all GISTs and 4 cases/million for malignant GISTs[14].Most GISTs are sporadic (not inherited) and have no clear cause, however, different risk factors associated with GISTs , like family history, where, family membersinherited a gene mutation that can lead to GISTs[15].

Familial gastrointestinal stromal tumor syndrome, is a rare, inherited condition that leads to increased risk of developing GISTs.

GISTS may be asymptomatic discovered accidentally by imaging or surgery for another disease,or by autopsy. Symptomatic cases presented with upper GIT bleeding as heamatemeses and malena due to breakdown of the covered mucosa. Intestinal obstruction, abdominal discomfort or pain ,Nausea, vomiting ,Feeling full after eating a small amount of food,Loss of appetite,weight loss and swallowing problems (for tumours in the esophagus) are not uncommon in these cases.

* FICMS,CABS
** FICMS,CABS

Diagnosis based on Imaging, such as abdominal or endoscopic ultrasonography, abdominal and pelvic CT scan and positron emission tomography (PET-CT), MRI , especially for rectal tumor. Upper and lower endoscopy.In majority of cases, a definitive diagnosis of GIST is made only after surgery. For inoperable or metastatic tumours biopsies should be taken, either by the percutaneous route or endoscopically and confirmed with histopathology studies, however, immunohistochemistry is the precise test to confirm diagnosis by pathologists where a part of the sample is treated with special manmade antibodies that will attach only to the KIT protein (also called CD117).[7,8].Recent studies have shown that the novel gene DOG1(diagnoses of GIST), which encodes for a chloride channel protein, is highly expressed in both *KIT* and *PDGFRA* mutant GISTs.[24-26]All GISTs tumours have the potential for malignant behaviour and gross examination of the tumour size and estimation of the mitotic count are essential in assessing prognosis.

The most common system used in staging of GISTs is the TNM system of the American Joint Committee onCancer (AJCC).

The overall relative 5-year survival rate of people diagnosed with a malignant GIST was estimated to be about 45%.

For Resectable disease treatment is a wide local resection with macroscopic and microscopic removal of the entire tumour is recommended (R0). Extended lymphadenectomy is usually not required. Some small tumours may be resected laparoscopically . When adjacent organs are involved, *en bloc* resection is recommended whenever possible. Endoscopic resection is not recommended. After ***resection*** Adjuvant therapy with imatinib may be considered in patients predicted to have a moderate to high risk of recurrence. [22,27,28]

For Unresectable/ Metastatic disease Imatinib should be used as treatment. However, Surgery may have a role at any stage in management and should be considered in patients with localised progression (i.e.<3 sites) to alleviate symptoms[22,27,28].

Follow-up following resection in very low risk tumours no imaging follow up required, in low risk tumours CT scan at 3 months following surgery, then clinical follow-up. In Moderate risk tumours CT scan at 3 months following surgery, then 6 monthly for 2 years, then annually to 5 years. In high risk tumours CT at 3 months following surgery, 3 monthly for 2 years, then 6 monthly for 2 years, then annually including chest, abdomen and pelvis[22,27,28].

Recurrence :multi-disciplinary team assesses tumour and carry out further resection ,start imatinib ,and/ or include clinical trial.Patients receiving adjuvant therapy with imatinib should have CT at 3 months after surgery, then 6 monthly for 2 years, then annually to 5 years (as per moderate risk)[22,27,28].

Patients and methods:

During period between January 2007 and January 2011,22patients with GIST tumor were involved in study in GIT hospital, 13 were male ,9 patients were female with medium age of 58 years old (37y.-71y.) .and oesophageal GISTs were excluded from this study.

Prior to surgery a full history and examination was taken with investigation including complete blood picture(C.B.P.), liver function tests, renal function tests and coagulation study according to the patient, in addition to CXR,and ECG.

Imaging tests used in the diagnoses were:-

1. Trans-abdominal ultrasonography for all patients.
2. Endoscopy:-
   a. Upper endoscopy(*esophogog-astroduodenoscopyor EGD*): for 13 patintswhich will review a submucosal mass or the mucosa may appear ulcerated especially if the patient presented with heamatemeses and malena
   b. Lower endoscopy (colonoscopy) : For 3 patients.
3. Abdominal and pelvicCTscan with iv and oral contrast in 13 patients.
4. Magnetic resonance imaging(MRI) in 5 patients.
5. Endoscopic U/S(EUS) was obtained for 10 patients of gastric mass and 2 patients of upper small bowel taken by one physician .

After doing laparotomy and the tumor excised then sent for histopathological examination where it is examined macroscopically and microscopically and if the tumour give a suspicion of GIST, staining of the tissue by special immunohistochemical stain (below) to differentiate the GIST from other mesenchymal tumour.

1. Monoclonal mouse Anti-Human c-kit Antigene.
2. Monoclonal mouse Anti-Human CD34 .
3. Monoclonal mouse Anti-Human S100.
4. Monoclonal mouse Anti-Human Desmin,

The usual hospital stay was 4-5 days, apart from one patient was 2weeks where she developed a high output fistula because her tumour was huge that need an extensive dissection with jujenoduodenal anastomoses, who later on died at ICU of another hospital.

When the patients discharged from the hospital, referred to the oncologist for adjuvant therapy by tyrosin kinase inhibitor (targeted therapy) like:-

1. imatinib mesylate(selective inhibitor) or
2. sunitinib(multitargeted inhibitor) if there is a resistance to the former.

CT scanwas done for each patient after surgery as a base line then every 3-6 months ,OGD for gastric tumour ,and colonoscopy for colonic tumour every 3-6 months.

Results:

This table shows that 13(59.09%) patients was males and 9(40.9%) were females, with a median age 57 years old (48y.-67y.).

Table(1)age and gender distribution

Age (years)	No.of patients
20-30	0
30-40	2(males)
40-50	13(5males,8females)
50-60	5(4males,1females)
70-80	2(males)

Eight of 14 patients of gastric tumour presented as upper GIT bleeding because of ulceration of the gastric mucosa,4 cases of small bowel presented with intestinal obstruction while the two cases who discovered accidentally ,one during open cholecystoctomy and the other by U/S for gynaecological complain and both cases are gastric tumour.

Table (2) clinical presentation

Clinical presentation	**No. of patients**
GIT bleeding	8(36.3%)
Abdominal pain	15(68%)
Intestinal obstruction	4(18%)
Change bowel habits	2(9%)
Asymptomatic	2(9%)

EUS had been taken for eleven patients with gastric tumours, where the lesion appear as hypoechoic mass arising from the muscularis properia , and all the cases of gastric tumour were diagnosed accurately by EUS(100%).

Table (3) endoscopic u/s (EUS) diagnoses

Site	**No.of patients**	**diagnoses**
Gastric	10	100%

Table (4) shows obviously that the main siteof GIST is the stomach,was 63.63%(14 patients),followed by the small bowel 18.8% then the colon with 9.09% while the rectum and the omentum had the same result 4.5%

Table (4) distribution according to the site

Site	NO.of patients	Percentage
Stomach	14	63.63%
Small bowel	4	18.8%
Colon	2	9.09%
Rectum	1	4.5%
Omentum	1	4.5%
Total	22	100%

Table (5) shows7(31.8%) patients of gastric neoplasm were with stage III where the tumour has high mitotic rate and larger than 10centimetre, Only one patient with Stage IA where the tumour was > 2 centimetre with low mitotic rate and the tumour discovered incidentally during operation for open cholecystectomy ,one patient with omental tumour presented with late symptoms which may explain its advanced staging (Stage IIIB).
Must patients with small and large bowel tumour had Stage IIIB where it is larger than 5 centimetre ,high mitotic rate .and patients with colonic and rectal tumour presented as change bowel habits and bleeding per rectum .

Table (5) stage distribution according to

Site	Stage IA	Stage IB	Stage II	Stage IIIA	Stage IIIB
Stomach	1	4	2	2	5
Omentum					1
Small bowel			2		2
Colon					2
Rectum					1

Table (6)shows postoperative morbidity where superficial thrombophlebitis is the most common (10 patients) and only one patient developed high out put Enterocutaneous fistula because the tumour was big that need extensive resection with jujenodoudenal anastomoses which end with fistula and the patient died lateron . Five patient had wound infection, 2 of them need drainage of abscess and the other three were minor ,all of them the wound healed within 4-9 days. Two patients of chest infection had atelacteses shown by CXR and treated by antibiotic and physiotherapy . Urinary tract infection presented as loin pain ,dysuria and fever ,proved by general urin examination and treated well by antibiotic

Table (6) complications following surgery

Types	No. of patients	Mortality
Thrombophlebitis	10	1(4.5%)
Chest infection	5	
Wound infection	5	
Urinary tract infection	3	
Enterocutaneous fistula	1	

Out of the 22 cases, 18 cases (81.82%) were positive for C-Kit and 4 cases (18.18%) were negative. (Fig.1). The positivity typically appeared as diffuse cytoplasmic staining with common membrane accentuation (fig.2) but, in some cases, was focally perinuclear, 'golgi zone-like staining(fig.3).
Cytoplasmatic staining were counted according to a 4-point semi quantitative scale (no staining 0-10% (0), weak 11-20% (1), moderate 21-50% (2), strong >50% (3)). A cutoff at 20% positivity in at least 10 HPF was used for prognostic analysis.
Ten of 18 cases were strong positive ,5cases were moderate and 4with weak positivity.

Figure(1) immunohistochemical staining distribution(C-kit marker)

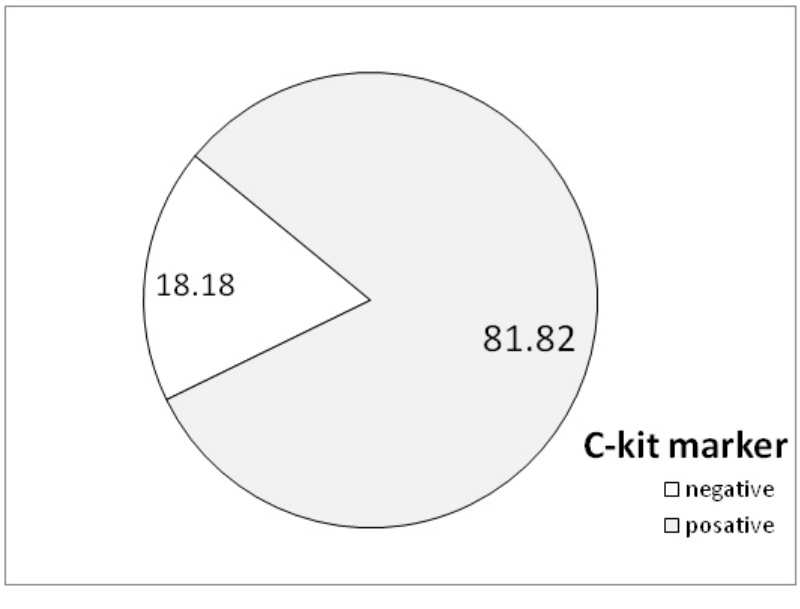
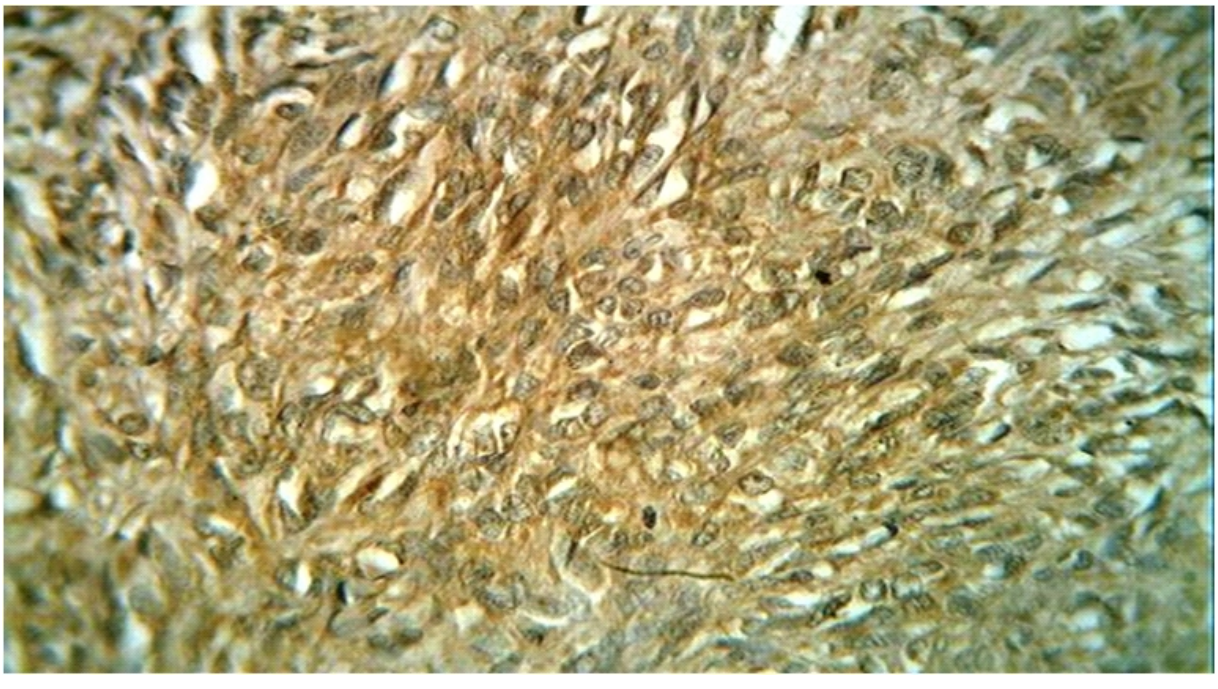


Figure (2):- Gastric section showing epithelioid cell histological subtype with high strong and moderate intensity for C-kit marker.



Figure(3):- Perinuclear pattern (Golgi pattern) of the C-Kit positivity

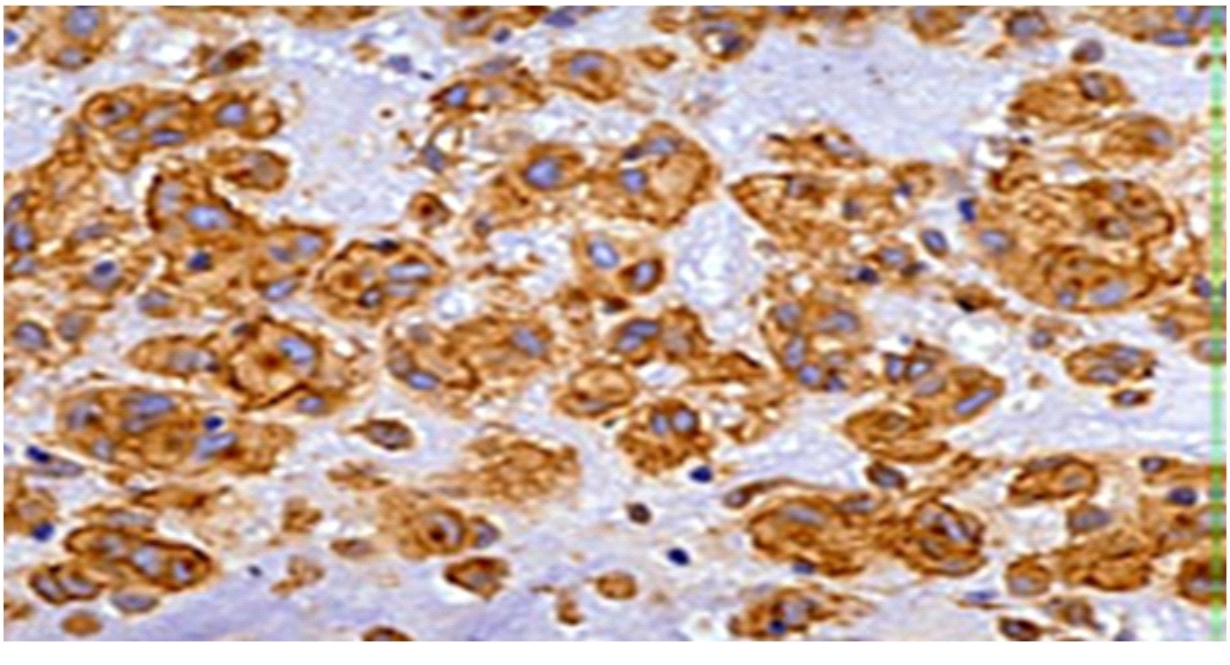


Figure (4) immunohistochemical staining distribution (CD-34marker:-.Thirteen (59.1%) of 22 cases were positive for CD-34marker,and 9(40.9%) Were negative.

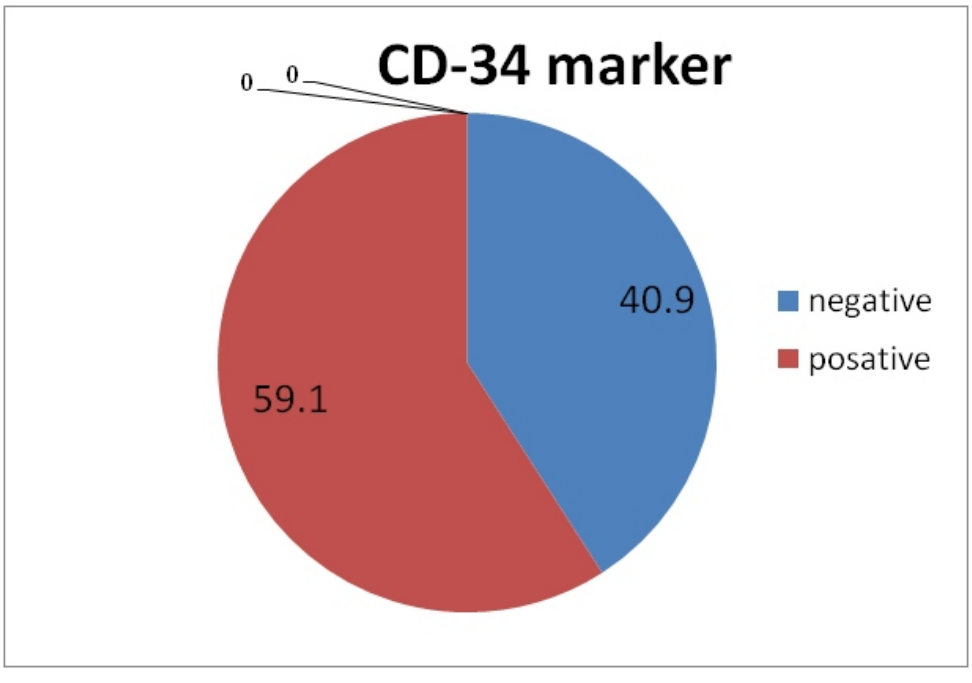


Figure (5) immunohistochemical staining distribution (S-100 marker):- Figure (5) showed that 17patients were negative(77.7%),and 5patients were positive(22.2%) for S-100 marker

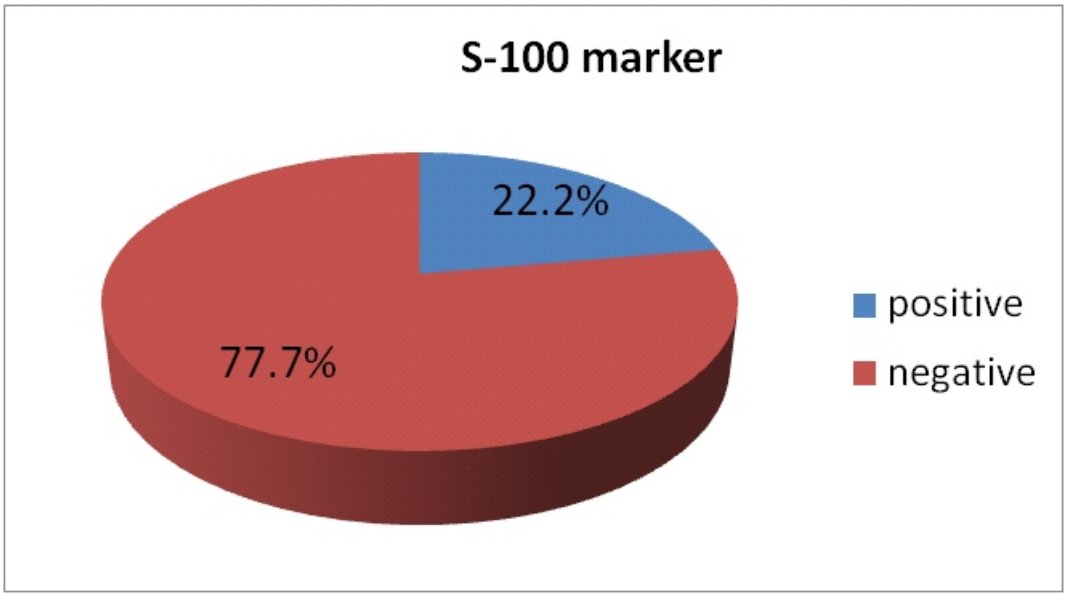


Figure (6) immunohistochemical staining distribution(desmin marker):- Three cases (13%) were positive for desminmarker,and 19cases were negative (87%).

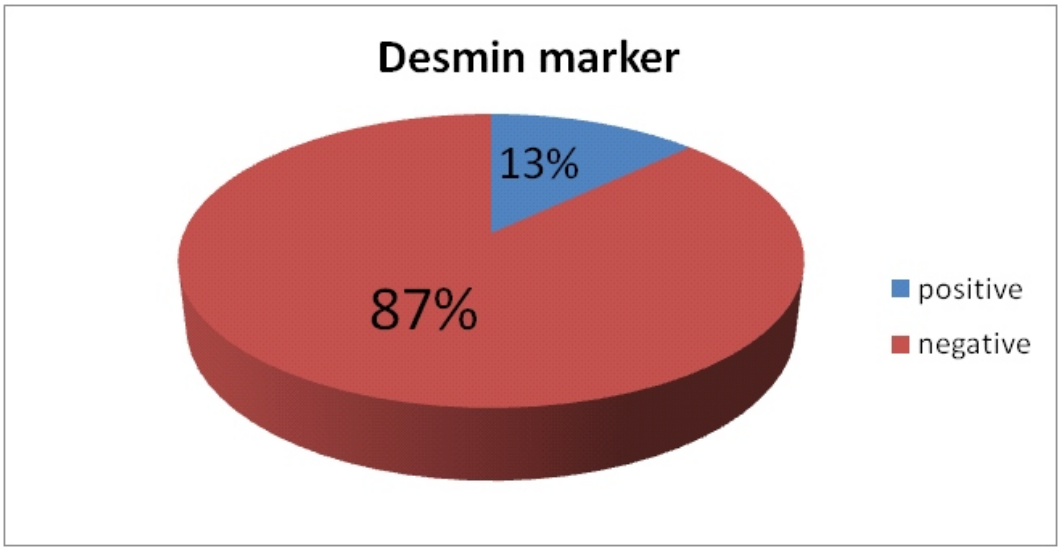


Table (7) distribution according to histological pattern :- The common histological type was spindle cell 10 cases(45.45%),followed by Epithelioid and mixed types were (31.8%) and (22.7%) respectively.

Type	No.of cases	Percentage
Spindle cell	10	45.45%
Epithelioid	7	31.8%
Mixed	5	22.7%
Total	22	100%

Table (8) types of surgical resection :-
Eleven cases were managed by local resection ,2cases by distal gastrectomy if the lesion was distally near the pylorus and only one case a median gastrectomy was done because the tumour was in the body and resection involving the lesser and the greater curvature with gastrogastrestomy. where the 7 cases of small and large bowel treated by resection with safety margin and restoration of the continuity by anastomoses .

Table (8) types of surgical resection

Site	No.of patients	Surgery
Stomach	14	Distalgastrectomy(2cases)
		Mediangastrectomy(1case)
		Local resection(11cases)
Small bowel	4	Segmental resection with end to end anastomoses
Omentum	1	Segmental resection
Colon	2	Resection with safety margin with anastomoses
Rectum	1	Anterior resection with anastomoses

Unfortunately only Sixteen patients were followed up within 2-36 months because of poor data registration in the archives. We found that 3patients had got recurrence ,one gastric lesion who developed a liver metastases shown by MRI within 8 months of surgery .The other two were small bowel and colonic tumour who got local recurrence within 15 months shown by CT scan.

Table (9) follow up (16 patients)

Age	**Site**	**Type of surgery**	**Duration of follow up(months)**	**Recurrence**
42	Stomach	Local resection	13	Clear by CTscan
44	colon	Local resection	26	Clear by CTscan
48	Small bowel	Local resection	32	Local recurrence
71	Small bowel	Local resection	23	Clear by CTscan
42	Stomach	Distal gastrectomy	6	Clear by CTscan
60	Stomach	Median gastrectomy	11	Clear by CTscan
49	Stomach	Local resection	8	Liver metastases
39	Stomach	Local resection	3	Clear by CTscan
64	Stomach	Local resection	25	Clear by CTscan
44	Stomach	Local resection	12	Clear by CTscan
58	Stomach	Local resection	10	Clear by CTscan
49	colon	Local resection	36	Local recurrence
41	Stomach	Local resection	19	Clear by CTscan
62	Stomach	Local resection	2	Clear by CTscan
47	Stomach	Distal gastrectomy	6	Clear by CTscan
53	Stomach	Distal gastrectomy	9	Clear by CTscan
All patients received imatinib as Adjuvant treatment				

Discussion:

GISTs is the most common mesenchymal neoplasm of the gastrointestinal tract . GISTs are under-diagnosed. In one study it was found 72% of cases now understood to be GISTs were classified previously as other tumours.[29]The morphological spectrum of GISTs is also wider than previously recognised.

In comparison to Miettinen M,lasota J et al[30,],and DeMatteo RP, Lewis JJ, Leung D et al[27],we found in our study that the main site of the tumour is the stomach(63.6%) versus(60%) for the former which is similarand (39%) for the last which is less .and the small bowel site was (18.8%) versus (35%)for the former and (32%) for the last. The median age was 57y. like the authers's result.The clinical presentation was abdominal pain(68%), GIT bleeding(36%) ,intestinal obstrution(18%)and asymptomatic (9%) in comparison to Reichardt P et al[31,32] where abdominal pain(20-50%), GITbleeding (50%), intestinal obstruction (10-30%),and (20%)was asymptomatic which may related to high quality of radiological investigation and higher education.Imagings are used for the diagnoses ,initial staging, restaging ,monitor response to therapy ,and perform a surveillance of possible recurrence .in our study the U/S,CTscan,MRI,and EUS are the main imaging modality available ,and the EUS is the most sensitive one in the diagnoses where it was(100%) for gastric tumour which is little less in comparison to other study done by Lau S, Tam KF, Kam CK et al.[33]

Surgery is the principal treatment of GISTs by which can produce curative resection with 2 centimetre safety margin[32,34],the aim of the surgery is resection with R0 margins and preservation of organ function ascan as possible but not on the expense of tumour free margins , 11outof 14 cases of gastric tumour had a local resection without lymph node dissection , one case need removal of satellite lesion near the pancreas which is proved another site of GIST ,and another patient need transverse colon resection to get R0 margins, 2patients with antral lesion managed by a distal gastrectomy with gastrojujenostomy,This study shows that the most of GISTs arising in the stomach with low or intermediate grade (68%),while it was high grade in (50%) of small bowel and (100%) for a large bowel that is consistent with study published byDeMatteo RP, Lewis JJ, Leung D et al.who showed gastric GISTs had more favourable prognoses than intestinal type[30]type[30]The current consensus among many pathologists is that the accurate diagnosis of GIST requires staining for c-Kit (CD117) expression.In our study(80.8%)of cases were positive c-Kit (CD117),and (18.18%)were negative which is less than what published by Fletcher CDM, Berman JJ, Corless C et al [23] and Miettinen M, Lasota J[14]where was (95%) positive and (5%)negative . The difference is related to limited number of cases and random selection. The expression of CD34 was 59% like in other studies of Fletcher CDM, Berman JJ, Corless C et al and Miettinen M, Lasota J[14,23] .The expression was especially in low grade ones, some recent studies revealed that ICC is the only GIT cells that are double positive for CD34 and CD117.Desmin and smooth muscle actin (SMA)are protein found in the smooth muscle tumours like leiomyosarcomas which are c-Kit negative, generally not found in the GISTs thereforethe positivity of these markers can differentiate the GISTs having smooth muscle from other muscle sarcomas. In our study was (13%) positive which is a little higher than other studies[14,23].

Follow up of patients need a good registration which is not always available making this section is difficult for assessment ,however in 16 cases who were followed up ,3(18%) of them had got recurrence observed by imaging studiesversus (40%) of 5years recurrence published byDematteoRP et al[32],this wide difference related to poor data available for accurate documentation and short periodstudy.

Relative low level of local recurrence gastric neoplasms related to low malignant potential of gastric GISTs.PET Scan can detect metabolic changes within the tumour in advance of visible changes on conventional imaging.[35]It may occasionally be used as part of a preoperative assessment, prior to planned resection of a large tumour, to exclude undetected distant metastases.

It is also useful in advanced stage disease, but may not detect tumours <2 cm diameter. If the patient has metastatic disease, with a positive PET scan, and is going to receive treatment with imatinib, then PET will provide a rapid means of determining the responsiveness of the tumour to imatinib, showing response much earlier than response can be seen on CT.[36] unfortunately this scan not available in our country because it is expensive and need special nuclear materials provided by nearby an atomic pile.

Conclusion:

GISTs are under estimated and its incidence is higher than what was expected, GISTs are diagnosed relying on histopathological features and immunohistochemical staining using CD117 ,CD34, S-100, Desmin, to differentiate the tumor from other mesenchymal neoplasms. Treatment with tyrosine kinase inhibitors are offering hope.Surgery remain the mainstay in treating the tumor.

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