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Nasir Ud Din

Aga Khan University, nasir.uddin@aku.edu

Zubair Ahmad

Aga Khan University, zubair.ahmad@aku.edu

Huma Arshad

Aga Khan University

Romana Idrees

Aga Khan University, romana.idrees@aku.edu

Naila Kayani

Aga Khan University, naila.kayani@aku.edu

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RESEARCH ARTICLE

Gastrointestinal Stromal Tumors: A Clinicopathologic and Risk Stratification Study of 255 Cases from Pakistan and Review of Literature

Nasir Ud Din*, Zubair Ahmad, Huma Arshad, Romana Idrees, Naila Kayani

Abstract

Purpose: To describe the clinicopathological features of gastrointestinal stromal tumors (GIST) diagnosed in our section and to perform risk stratification of our cases by assigning them to specific risk categories and groups for disease progression based on proposals by Fletcher et al and Miettinen and Lasota. **Materials and Results:** We retrieved 255 cases of GIST diagnosed between 2003 and 2014. Over 59% were male. The age range was 16 to 83 years with a mean of 51 years. Over 70% occurred between 40 and 70 years of age. Average diameter of tumors was 10 cms. The stomach was the most common site accounting for about 40%. EGISTs constituted about 16%. On histologic examination, spindle cell morphology was seen in almost of 85% cases. CD117 was the most useful immunohistochemical antibody, positive in 98%. Risk stratification was possible for 220 cases. Based on Fletcher's consensus proposal, 62.3% gastric, 81.8% duodenal, 68% small intestinal, 72% colorectal and 89% EGISTs were assigned to the high risk category; while based on Miettinen and Lasota's algorithm, about 48% gastric, 100% duodenal, 76% small intestinal, 100% colorectal and 100% EGISTs in our study were associated with high risk for disease progression, tumor metastasis and tumor related death. Follow up was available in 95 patients; 26 were dead and 69 alive at follow up. Most of the patients who died had high risk disease and on average death occurred just a few months to a maximum of one to two years after initial surgical resection. **Conclusions:** Epidemiological and morphologic findings in our study were similar to international published data. The majority of cases in our study belonged to the high risk category.

Keywords: Gastrointestinal stromal tumor - extra gastrointestinal tumor - risk stratification - Pakistan

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Introduction

Gastrointestinal stromal tumors (GISTs) are a heterogeneous group of tumors which comprise the most common primary mesenchymal tumors of the gastrointestinal tract (GIT) and occur throughout the GIT from esophagus to rectum (Rubin, 2006; Leigl-Atzwangar, et al., 2012). The commonest site for GISTs is stomach (approximately 60%) followed by small intestine (excluding duodenum) (Nilsson et al., 2005; Miettinen et al., 2010). About 85-90% GISTs harbor a mutation of KIT (CD117), a tyrosine kinase receptor which is normally expressed by the 'pacemaker' interstitial cells of cajal located in the wall of the gut. These cells coordinate the autonomic nervous system of the gut and the smooth muscle cells to regulate motility and peristalsis. Most GISTs therefore originate in the submucosa or muscularis propria. The remaining 5 to 15% GISTs contain PDGFRA activity mutations (Heinrich et al, 2002; Hornick and Fletcher, 2004). The KIT mutation results in the activation of the Tyrosine kinase receptor allowing the detection of KIT (CD117) mutation by immunohistochemistry and

helps in confirming the histologic diagnosis of GIST (Heinrich et al., 2002; Coindre et al., 2005; Zhang et al., 2009; Miettinen et al., 2010). Most patients are elderly, median age ranges between 58 and 66 years (Coindre et al., 2005; Tryggvason et al., 2005; Cao et al., 2010; Miettinen et al., 2010). However, no definite gender predilection has been reported. Histologically, most tumors in all sites show a spindle cell appearance (75 to 80%), while epithelioid cell or mixed morphology is seen in minority of cases (Coinder et al., 2005; Miettinen and Lasota, 2006; Miettinen et al., 2010). Small intestinal GISTs are twice as likely to behave as clinically malignant tumors compared to gastric GISTs, while most colorectal GISTs are very aggressive and advanced tumors with a poor prognosis (Mittinen et al., 2010a; 2010b).

GISTs can also occur outside the GIT mainly in the omentum, mesentery and retroperitoneum where they need to be distinguished from other mesenchymal tumors, especially from benign and malignant smooth muscle tumors (Reith et al., 2000).

The most important prognostic factors on the basis of which GISTs are categorized into distinct prognostic

Department of Pathology and Microbiology, Section of Histopathology, Aga Khan University Hospital, Karachi, Pakistan *For correspondence: nasir.uddin@aku.edu

groups are tumor size and number of mitoses per 50 high power fields (HPFS) (Miettinen et al., 2010). The consensus proposal by Fletcher et al. (2002) combined these two (size and mitotic activity) to divide GISTs into risk categories, while Miettinen and Lasota also added the anatomic location to provide comprehensive information about the prognosis (Miettinen and Lasota, 2006).

The aim of our study was to present the epidemiologic data of our cases, describe the morphologic (including Immunohistochemical) features, and perform risk stratification by assigning our cases into specific risk categories and groups based on both the consensus proposal (Fletcher et al., 2002) and the more elaborate risk prediction algorithm (Miettinen and Lasota, 2006). Follow up, where available, was taken and recorded.

Materials and Methods

A total of 255 cases (stomach, duodenum, small intestine, colorectal and extra gastrointestinal) diagnosed in the Section of Histopathology, Aga Khan University Hospital, Karachi between the years 2003 and 2014 were included in the study. Clinical data such as age, gender, tumor location, tumor size, signs and symptoms and follow up were recorded. Histological features including spindle cell or epithelioid or mixed pattern and mitotic activity per 50 HPFs were noted. Immunohistochemical reactivity to the following antibodies was noted: CD117, CD34, DOG

Table 1. Decade Wise Age Distribution of our Cases (n=255)

S No.	Decade	Number	Percentage%
1	11-20	2	0.80%
2	21-30	13	5.10%
3	31-40	33	12.90%
4	41-50	58	22.70%
5	51-60	59	23.10%
6	61-70	62	24.30%
7	71-80	25	9.80%
8	>80	3	1.20%

Table 2. Site Wise Distribution of our Cases (n=255)

S No.	Site	Number	Percentage%
1	Esophagus	1	0.40%
2	Stomach	117	45.90%
3	Duodenum	14	5.50%
4	Jejunum	22	8.60%
5	Ileum	34	13.30%
6	Colorectum	26	10.20%
7	Mesentery	23	9.10%
8	Retroperitoneum	10	3.90%
9	Omentum	8	3.10%

Table 3. Immunohistochemical Profiles of Cases in our Study (n=255)

S No.	Immunohistochemical antibody	Positive	Focal positive	Negative	Not performed
1	CD 117	242 (94.9%)	8 (3.1%)	5 (2%)	---
2	CD 34	169 (70.4%)	14 (5.8%)	57 (23.8%)	15
3	DOG 1	18 (72.0%)	2 (8%)	5 (20%)	230*
4	Smooth Muscle Actin (ASMA)	67 (29.4%)	45 (19.7%)	116 (50.9%)	27
5	S 100 protein	64 (30.3%)	29 (13.7%)	118 (56%)	44

*acquired in 2013

1, Anti- Smooth muscle Actin (ASMA) and S100 protein.

Risk stratification was performed using tumor location, tumor size and mitotic activity / 50 HPFs, and the cases were assigned to specific risk categories and groups.

Statistical analysis was performed using SPSS 19.0 version.

Results

A total of 255 cases were included. Age of the patients ranged from 16 to 83 years with mean and median age of 51 and 52 years respectively. The decade wise distribution is shown in Table 1. As shown in this table, over 70% were between 40 and 70 years of age. Out of 255, 151 (59.2%) patients were males, and 104 (40.8%) were females. Male: female ratio was 1.4:1. Of the 255 cases, 35 (13.7%) were small core biopsies while 220 (86.3%) were resection specimens. The size of the tumors ranged from 2.0 cms to 26 cms with an average size of 10 cms in the largest dimension.

Stomach was the commonest site in our series followed by the small intestine. The site wise breakup is shown in Table 2. Almost 46% of all cases were located in the stomach while over 27% were located in the small intestine. Extra GI GISTs comprised 41 cases (16.10%).

Grossly, majority of tumors were submucosal or intramural, nodular bulging masses, many with central ulceration. Some were polypoid and protruded into the gastric lumen (Figure 1A,B). Majority of our small intestinal and colorectal GISTs were polypoid with protrusion into the lumen and were less commonly intramural.

Out of 255 cases, 216 (84.7%) showed spindle cell morphology, 32 (12.5%) showed epithelioid morphology, while 7 cases (2.7%) were mixed (Figure 2A,B).

Immunohistochemistry was performed on most cases (Figure 3A,B). The antibodies employed and immunohistochemistry results are summarized in Table 3. The antibody DOG1 was acquired in 2013. Hence, this antibody was used only in the recently diagnosed cases.

Risk stratification and assigning of cases into specific risk categories and groups was done based on the studies (Fletcher et al., 2002; Miettinen and Lasota, 2006). Risk stratification was not possible on 35 cases as these were small core biopsies. It was thus performed on 220 cases. These included 98 out of 117 cases of gastric GIST, 50 out of 56 cases of jejunal and ileal GISTs, 11 out of 14 cases of duodenal GISTs, 25 out of 27 cases of colorectal GISTs, and 36 out of 41 cases of extra GI GISTs. The findings are shown in Tables 4 and 5.

Follow up was available in 95 out of 220 cases. Of these 95 patients, 69 are alive, while 26 patients died.

Table 4. Risk Stratification. Assignment of Cases in our Series into Risk Categories Based on Fletcher et al's Proposal(18) (n=220)

S. No.	Site	Number	Very Low Risk *	Low Risk **	Intermediate Risk ***	High Risk ****
1	Stomach	98	3 (3.1%)	17 (17.3%)	17 (17.3%)	61 (62.3%)
2	Duodenum	11	---	---	2 (18.2%)	9 (81.8%)
3	Jejunum + Ileum	50	---	5 (10%)	11 (22%)	34 (68%)
4	Colorectum	25	---	2 (8%)	5 (20%)	18 (72%)
5	Mesentery	19	---	---	1 (5.3%)	18 (94.7%)
6	Retroperitoneum	13	---	---	3 (23.1%)	10 (76.9%)
7	Omentum	4	---	---	---	4 (100%)

*> 2 cms, > 5 M / 50 HPF; **2-5 cms, > 5 M / 50 HPF; ***<5 cms, 6-10 M / 50 HPF; or 5-10 cms, < 5 M / 50 HPF; ****>5 cms, > 5 M / 50 HPF; or > 10 cms, any no. of mitoses; or any size, > 10 M / 50 HPF

Table 5. Risk Stratification. Assignment of Cases in our Series into Risk Groups Based on Miettinen and Lasota's Algorithm(14) (n=220)

S. No.	Site	Number	Group 1	Group 2	Group 3 ^a	Group 3 ^b	Group 4	Group 5	Group 6 ^a	Group 6 ^b
1	Stomach	98	5 (5.1%)	15 (15.3%)	10 (10.2%)	8 (8.2%)	---	13 (13.3%)	20 (20.4%)	27 (27.5%)
2	Duodenum	11	---	---	1 (9.1%)	---	---	1 (9.1%)	1 (9.1%)	8 (72.7%)
3	Jejunum+Ileum	50	---	5 (10%)	7 (14%)	13 (26%)	---	4 (8%)	7 (14%)	14 (28%)
4	Colorectum	25	---	---	2 (8%)	3 (12%)	---	7 (28%)	6 (24%)	7 (28%)
5	EGISTs	36	---	---	2 (5.5%)	6 (16.7%)	---	2 (5.5%)	3 (8.3%)	23 (63.9%)

*Group 1:> 2 cms, < 5 M / 50 HPF; Group 2: 2-5 cms, < 5 M / 50HPF; Group 3^a:5-10 cms, < 5 M / 50HPF; Group 3^b:>10 cms, < 5 M / 50HPF; Group 4:<2 cms, > 5 M / 50HPF; Group 5:2-5 cms, > 5 M / 50HPF; Group 6^a:5-10 cms, > 5 M / 50HPF; Group 6^b:> 10 cms, > 5 M / 50HPF

Table 6. Data of Patients who were Dead at Follow Up (n=26)

S. No.	Site	Risk Category	Group	Gleevec Status	Year of Surgery	Year of Death
1	Retroperitoneum	High	6b	No	2004	2006
2	Jejunum	High	6b	Yes	2004	2007
3	Stomach (a)	High	6b	Yes	2004	2006
4	Stomach	High	6a	Yes	2005	2005
5	Stomach	High	6b	Yes	2005	2007
6	Colorectum	High	6a	Yes	2006	2006
7	Jejunum (b)	Moderate	3a	Yes	2006	2012
8	Duodenum	High	6a	No	2006	2006
9	Retroperitoneum (c)	High	6b	No	2008	2008
10	Colorectum (d)	High	6b	Yes	2009	2011
11	Stomach (e)	High	6b	Yes	2009	2009
12	Colorectum (f)	High	6b	Yes	2009	2011
13	Jejunum (g)	High	6b	No	2009	2009
14	Retroperitoneum (h)	High	6b	Yes	2009	2010
15	Stomach (i)	Moderate	5	No	2010	2011
16	Stomach	High	6b	No	2010	2010
17	Mesentery	High	6b	No	2011	2012
18	Mesentery	High	6a	No	2011	2011
19	Colorectum	High	6b	No	2011	2013
20	Ileum	High	6a	Yes	2011	2012
21	Stomach (j)	High	6b	No	2012	2012
22	Stomach (k)	Very Low	2	No	2012	2012
23	Duodenum (l)	High	6a	Yes	2012	2012
24	Stomach (m)	Moderate	5	Yes	2013	2014
25	Retroperitoneum (n)	High	6b	Yes	2013	2013
26	Stomach	High	6a	Yes	2013	2014

* Note: Additional information available: (a) Metastasis to kidney and heart, died in 2006; (b) Took Gleevec continuously, no history of recurrence or metastases; (c) Died immediately after surgery; (d) Took Gleevec regularly, died during surgery for excision of recurrent tumor; (e) Took Gleevec regularly until death seven months after surgery; (f) Took Gleevec regularly until death two years after surgery; (g) Died immediately after surgery; (h) Took Gleevec regularly until death six months after surgery; (i) Died of liver failure in 2011 (had chronic Hepatitis C); (j) Died soon after surgery; (k) Very low risk disease, died three months after surgery from widespread metastases of concomitant colorectal adenocarcinoma; (l) Died four months after surgery, took Gleevec regularly; (m) Took Gleevec regularly, died about one year after surgery, possibly due to some unrelated cause; Took Gleevec regularly until death four months after surgery

Of the latter, 1 patient had a very low risk gastric GIST. However, he had a concomitant gastric adenocarcinoma with positive lymph nodes, and died as a result of complications secondary to the adenocarcinoma. Of

the remaining 25 patients, 22 had high risk while 2 had moderate risk disease. The disease was located in the stomach in 10 cases, small intestine (ileum and jejunum) in 4 cases, duodenum in 2 cases and colorectum in 4

Table 7. Data of Patients who were Alive at Follow Up-Site wise Breakup (n=69)

Site	No. of Cases	Year Resected										Treated with Gleevec		Risk Category						
		2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Yes	No	V. low risk	low risk	Inter-mediate risk	High risk	Recur-rence	Meta-stases
Esophagus	1	-	-	-	-	-	-	-	-	-	1	-	-	-	1	-	-	-	-	-
Stomach	32	1	-	-	-	-	1	4	9	5	12	-	23	9	2	4	9	17	1	4
Duodenum	1	-	-	-	-	1	-	-	-	-	-	-	1	-	-	-	-	1	-	-
Small Intestine (Jejunum+Ileum)	19	-	2	1	-	1	3	6	2	2	2	-	13	6	-	1	5	13	1	1
Colorectum	10	-	-	-	-	-	1	3	2	3	1	-	8	2	-	-	5	5	2	1
EGISTs	6	-	-	-	-	-	1	1	3	-	1	-	6	-	-	-	3	3	-	-

of these 69 patients are given in Table 7.

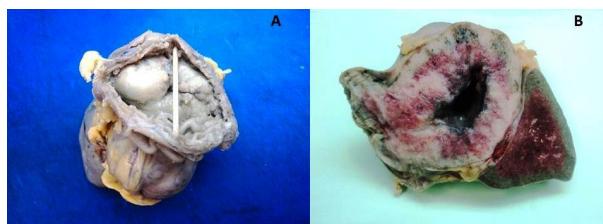


Figure 1. A) Gross Appearance of GIST of Stomach Protruding into the Lumen; B) GIST of Stomach with a Fleshy Cut Surface

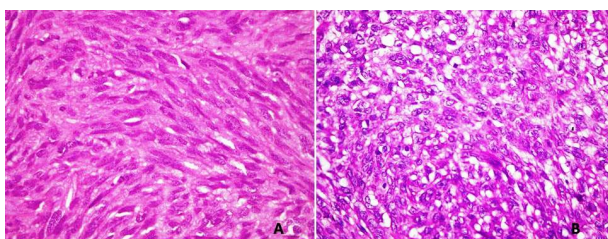


Figure 2. A) Spindle cell GIST Arranged in Fascicles. B) Sheets of Epithelioid Cells with Eosinophilic Cytoplasm in Epithelioid GIST

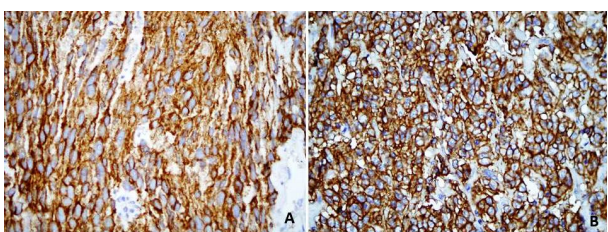


Figure 3. CD117 (A) and DOG 1 (B) Positivity in GIST

cases, while 6 cases represented EGISTs. Out of the 26 patients, 15 had been treated with Gleevec, while 11 did not receive this treatment. The details of these 26 patients are given in Table 6.

Out of the 69 patients who are still alive, 47 had high risk disease, 15 had intermediate risk, 5 had low risk and 2 patients had very low risk disease. Of these 69 patients, 4 patients had one or more recurrences and 6 had metastatic disease at the time of follow up. The disease was located in the stomach in 32 out of 69 cases, in the small intestine (ileum and jejunum) in 19 cases, duodenum in 1 case, colorectum (including anal region) in 10 cases, and esophagus in 1 case, while EGISTs accounted for 6 cases. Out of the 69 patients, 52 had been treated with Gleevec, while 17 patients did not receive this treatment. The details

Discussion

In 2013, we published an epidemiological and histological perspective of diseases of the gastrointestinal tract in Pakistan (Ahmad et al., 2013). In the current article, an epidemiological, histological and risk stratification perspective of GIST is presented.

As shown in the results, mean age was 51 years and the highest number of cases were diagnosed in the fifth, sixth and seventh decades (Table 1). The mean age is much lower in our series than reported in Western and even Asian literature where mean ages of gastric and small intestinal GISTs have varied from 58 to 70 years (Coindre et al., 2005; Tryggvason et al., 2005; Cao et al., 2010; Miettinen et al., 2010; Wang et al., 2013). GISTs in all locations occur in the elderly, less than 10% gastric GISTs occur in patients below 40 years of age (Miettinen and Lasota, 2006). In our study, almost 19% GISTs occurred below the age of 40 years (Table 1). Studies have shown no gender predilection, although some studies demonstrate a mild male predominance i.e. 52 to 55% in GISTs in all locations (Cao et al., 2010; Miettinen et al., 2010). In our study, over 59% patients were males. The average size of tumors in our study was 10 cms and size ranged from 2 to 26 cms. Various studies have reported sizes ranging from a few millimeters to greater than 20 cms for small intestinal, and a few millimeters to greater than 40 cms for gastric GISTs (Miettinen and Lasota, 2006). In the largest series of gastric GISTs published (Miettinen et al., 2005), the mean size for gastric GISTs was 6 cms. In two separate studies, from Iceland and China, mean tumor size was 4.6 cms and 7.02 cms respectively (Tryggvason et al., 2005; Cao et al., 2010). Symptoms in our cases were variable; the commonest were vague abdominal pain, abdominal mass, heart burn, bleeding per rectum, hematemesis, anemia etc. Grossly, majority of our gastric tumors were submucosal or intramural, nodular bulging masses, many with central ulceration. Some were polypoid and protruded into the gastric lumen. Majority of our small intestinal and colorectal GISTs were polypoid with protrusion into the lumen and were less commonly intramural. Similar, gross appearances have been described by various authors (Rosai, 2003; Miettinen and Lasota, 2006).

In our series, stomach was the commonest site, (almost 46%), while almost 22% were located in the small intestine (jejunum and ileum excluding duodenum). If duodenum

is included, over 27% cases were located in the small intestine (Table 2). According to various international studies, 59 to 61% GISTs occur in stomach (Nilsson et al., 2005; Tryggvason et al., 2005; Miettinen et al., 2006), about 30% in the jejunum and ileum, and 4 to 5% occur in the duodenum (Miettinen et al., 2003). Colorectal GISTs comprise 4 to 5% (Miettinen et al., 2006; Cao et al., 2010). Compared to the international data, location in stomach and small intestine was slightly less common in our series while location in colon and rectum was slightly higher. However, a recent study from Turkey reported tumor location in the stomach in 45.6% cases, very similar to our findings (Selcukbiricik et al., 2013).

On histological examination, almost 85% cases showed spindle cell morphology while cases with epithelioid morphology comprised over 12%. Various international studies have reported the epithelioid type to comprise between 20-25%, with mixed tumors comprising the remaining 5 to 10% cases (Coinder et al., 2005; Miettinen et al., 2006; Miettinen et al., 2010).

Immunohistochemically, CD117 was the most useful antibody, being strong diffuse positive in almost 95%. CD 34 showed diffuse strong positivity in over 70%. We have limited experience with DOG1 since we acquired this antibody only in 2013. It demonstrated diffuse positivity in 72%. We intend to use DOG1 in all future cases as this antibody has proved to be a very sensitive and specific marker for GISTs (Miettinen et al., 2009). Anti-Smooth Muscle Actin (ASMA) was diffuse or at least focal positive in about 49% cases, while S100 protein was diffuse or focal positive in 44% cases (Table 3).

Published Western literature shows that CD117 positivity is seen in 95% (gastric) to 98% (small intestinal) GISTs, and CD34 positivity in 60-70% GISTs. However, CD34 positivity varies with positivity seen in 80 to 85% gastric, 50% small intestinal and 95 to 100% esophageal and colorectal GISTs. It has been seen that most spindle cell GISTs shown positivity for CD34 (Coinder et al., 2005; Miettinen et al., 2005; Miettinen and Lasota, 2006; Miettinen et al., 2006). A study from China showed CD117 positivity in 94.5% and CD34 positivity in 86.2% cases (Cao et al., 2010). Another Asian study showed CD117 and DOG 1 positivity in 90.5% and 84.1% cases respectively (Sun et al., 2012).

With regard to ASMA and S100 protein, positivity for the former has been reported in 20% of gastric and 35% of small intestinal GISTs, while positivity for the latter has been reported rarely (<1%) in gastric GISTs. However, positivity for S100 protein has been very variable with various studies reporting positivity in 14% to 50% cases. Studies have demonstrated that CD34 expression is not a significant prognostic factor for gastric and small intestinal GISTs. However, ASMA expression is a statistically significant favorable prognostic factor in gastric and small intestinal GISTs (Tworek et al., 1997; Miettinen et al., 2005; Miettinen et al., 2006). The prognostic and predictive potential of immunohistochemical stains in GIST has been studied but results are conflicting and inconclusive (Sun et al., 2012; Demir et al., 2013).

Over 16% cases in our series were diagnosed as extra gastrointestinal GISTs (EGISTs) and most of these

were high risk (Tables 4&5). While EGISTs definitely represent bona fide and true GISTs, and demonstrate CD117 immunohistochemical expression as well as GIST-specific KIT mutations (Rosai et al., 2004; Yamamoto et al., 2004; Miettinen et al., 2013), their incidence in most series is extremely low, around 1% (Miettinen and Lasota, 2006). One study did not find a single convincing case among 200 cases (Agaimy and Wunsch, 2006). However, EGISTs comprised 10% of all GISTs in a study from Korea (Cho et al., 2010). The current concept is that most so called EGISTs are actually detachments or metastases from GISTs of primary gastrointestinal tract origin (Miettinen and Lasota, 2006; Miettinen et al., 2013). We get a lot of referral cases from all over Pakistan, a large country with a population of 190 million, and accurate surgical details or radiological films are not available in many cases. It is quite possible that many of the so called EGISTs in our series actually represent involvement of retroperitoneum, omentum, mesentery etc by gastrointestinal stromal tumors. Studies have looked for parameters that can clearly identify bona fide EGISTs. Matrix metalloproteinases (MMPs), which are molecules that are implicated in metastasis by various malignant tumors, have been investigated for their role in contributing to the ability of EGISTs to metastasize. A recent study demonstrated that increased MMP-2 and MMP-9 expression was associated with increased risk of metastasis and aggressive behavior in E-GISTs (Wang et al., 2014).

The evaluation of prognosis is essential in GIST. Every GIST carries a risk and potential for malignant behavior and there is increasing reluctance to label any GIST as benign. However, this risk varies from very low to very high (Coinder et al., 2005; Miettinen et al., 2013). Earlier studies showed that about 50% primary localized GISTs relapsed within the first five years (local recurrence within the peritoneal cavity or liver metastases) while a much greater percentage of GISTs relapsed within ten years, and that if relapse occurred, prognosis was almost invariably poor (Franquemont, 1995; Emory et al., 1999; DeMatteo et al., 2000). It became increasingly clear that it was not practically possible to divide GISTs into benign or malignant categories based on morphology alone and the emphasis shifted to determining criteria which could assess the risk of GISTs to behave in a malignant fashion. Several schemes were developed to define criteria which can stratify the risk of malignant behavior and by which GISTs can be assigned to definite risk categories (low, intermediate, high) or groups (Franquemont, 1995; Fletcher et al., 2002; Miettinen and Lasota, 2006). Tumor size and number of mitoses per 50/HPFs emerged as the major criteria. It also became clear that location was extremely important, with non-gastric GISTs harboring a much higher risk for malignant behavior compared to gastric GISTs of comparable size and mitotic activity (Tryggvason et al., 2005; Miettinen and Lasota, 2006). Other histologic factors including cellularity, coagulative necrosis, mucosal invasion etc have been suggested (Miettinen et al., 2005; Tryggvason et al., 2005; Miettinen et al., 2006). Currently, the risk stratification is based on the consensus proposal (Fletcher et al., 2002) and the risk

prediction algorithm (Miettinen and Lasota, 2006). Based on these, over 62% of gastric, almost 82% duodenal, 68% small intestinal (jejunum and ileum), 72% colorectal, 95% mesenteric, 77% retroperitoneal and 100% omental GISTs in our series belonged to high risk category (Table 4). In a recent study from Turkey which looked at 249 cases, 47% cases belonged to the high risk category (Selcukbiricik et al., 2013). Other recent studies from Asia have also risk stratified GISTs based on the above criteria (Chen et al., 2013). High risk tumors made up 70% and 60% respectively of all cases in two studies from India (Lakshmi et al., 2010; Ravikumar et al., 2011).

Table 4 also shows that 3% of all gastric GISTs fell into the very low risk category, while 17.3% each fell into low risk and intermediate risk categories. Among jejunal and ileal GISTs, 10% and 22% fell into low risk and intermediate risk categories respectively, while 8% and 20% colorectal GISTs fell into the low and intermediate risk categories. Of the so called EGISTs in our series, just over 5% of mesenteric and 23% retroperitoneal GISTs fell into the intermediate risk category.

Based on Miettinen and Lasota's study (Miettinen and Lasota, 2006), over 5% of gastric GISTs in our study fell into 'Group 1' which is not associated with any risk for progressive disease, tumor metastases and /or tumor related death. These were the only tumors in our study which fell in group 1 (Table 1). Over 15% of gastric and 10% of jejunal and ileal GISTs in our study fell into 'Group 2' which is associated with very low risk for progressive disease, metastases and tumor related death for gastric and low risk for GISTs in all other locations. Just over 10% gastric and 9% duodenal GISTs, 14% small intestinal (jejunal and ileal), 8% colorectal, and over 5% EGISTs fell in 'Group 3a' which is associated with low risk for gastric and moderate risk for ileal and jejunal GISTs. Slightly over 8% gastric, 26% small intestinal (jejunal and ileal), 12% colorectal and almost 17% EGISTs fell in 'Group 3b' according to Miettinen's algorithm. Group 3b is associated with moderate risk for gastric and high risk for jejunal and ileal GISTs. Miettinen and Lasota (Miettinen and Lasota, 2006) combined groups 3a and 3b in duodenal and colorectal GISTs due to small number of cases and the 'Combined group 3' is associated with high risk for duodenal and rectal GISTs. No tumor in our study fell into 'Group 4'. Over 13% gastric, over 9% duodenal, 8% small intestinal, 28% rectal and over 5% EGISTs in our study fell in 'Group 5' which is associated with moderate risk for gastric and high risk for all other locations. Over 20% gastric, over 9% duodenal, 14% jejunal and ileal, 24% colorectal and over 8% EGISTs in our study fell into 'Group 6a' which is associated with high risk for gastric as well as jejunal and ileal GISTs. Over 27% gastric, almost 73% duodenal, 28% small intestinal (jejunal and ileal), 28% colorectal and almost 64% EGISTs in our study fell into 'Group 6b' which is associated with high risk for gastric as well as Jejunal and Ileal GISTs. Miettinen and Lasota (Miettinen and Lasota, 2006) combined groups 6a and 6b in duodenal and rectal GISTs due to small number of cases and the 'Combined Group 6' is associated with high risk for duodenal and colorectal GISTs. Jejunal and ileal, duodenal and rectal GISTs in groups 5, 6a and 6b, and

gastric GISTs in groups 6a and 6b all carry a high risk for progressive disease, metastases and tumor related death. Gastric GISTs in groups 3b and 5 and jejunal and ileal GISTs in group 3a carry a moderate risk for progressive disease; gastric GISTs in group 3a, jejunal and ileal, duodenal and colorectal GISTs in group 2 carry a low risk for progressive disease; while gastric GISTs in group 2 carry a very low risk for progressive disease, tumor metastasis and tumor related death (Miettinen and Lasota, 2006). Earlier studies by Miettinen et al (Miettinen et al., 2005; Miettinen et al., 2006) showed that about 16%, 55% and 86% of gastric GISTs in groups 5, 6a and 6b; 73%, 85% and 90% of jejunal and ileal GISTs in groups 5, 6a and 6b; 50% duodenal and 52% rectal GISTs in group 5; while 86% duodenal and 71% rectal GISTs in combined group 6 developed progressive disease, tumor metastases and tumor related death.

Based on Fletcher et al.'s consensus approach (Fletcher et al., 2002), about 38% gastric GISTs in our study (Tables 4 & 5) were assigned to the very low, low and intermediate risk categories while 62% are assigned to the high risk category. Using the more elaborate algorithm, developed by Miettinen and Lasota (Miettinen and Lasota, 2006), about 52% of gastric GISTs in our study were assigned groups 1, 2, 3a, 3b and 5 which are associated with no risk (group 1), very low risk (group 2), low risk (group 3a) and moderate risk (group 3b and 5) and the remaining 48% gastric GISTs were assigned groups 6a and 6b which are associated with high risk for disease progression, metastasis and tumor related death (Fletcher et al., 2002). About 18% of duodenal GISTs in our series were assigned the intermediate risk category while 82% were assigned the high risk category. However, all our duodenal GISTs were assigned to groups 3, 5 and 6 all of which are associated with high risk in duodenal GISTs. About 10% of small intestinal (jejunal and ileal) GISTs were assigned to the intermediate risk, and 68% were assigned to the high risk category. However, based on Miettinen and Lasota's proposal (Miettinen and Lasota, 2006), 10% small intestinal GISTs in our study were assigned group 2 (low risk), 14% were assigned group 3a (moderate risk) and the remaining 76% were assigned groups 3b, 5, 6a and 6b all of which are associated with high risk for disease progression in jejunal and ileal GISTs. Based on Fletcher's proposal [18], 8% and 72% of colorectal GISTs were assigned to the low risk and high risk category respectively. Based on Miettinen's algorithm (Miettinen and Lasota, 2006), all colorectal GISTs were assigned groups 3, 5 and 6 all of which are associated with high risk in colorectal GISTs.

About 11% EGISTs in our study were assigned to the intermediate risk and 89% to high risk category, but all were assigned groups 3, 5 and 6 which are associated with high risk of tumor progression in EGISTs.

The primary treatment of GISTs is surgical excision with adequate negative tumor margins. All patients in our series underwent resection, with negative surgical margins in all but 4 patients.

Although surgical excision is the mainstay of therapy for GISTs, targeted therapy with Imatinib mesylate (Gleevec) which binds to KIT and inhibits intracellular

signaling, has shown spectacular results especially in patients with unresectable, recurrent and even metastatic tumors (Mechtersheimer et al., 2004). Although there is still no agreement on whether it should be given in the adjuvant or neoadjuvant setting, some authorities now recommend adjuvant treatment if the chances of recurrence are greater i.e. large tumor size, location other than gastric, high mitotic rate etc. Treatment is recommended for at least a year after surgery, while for tumors which are highly likely to recur, treatment is recommended for up to three years after surgery. A recent study showed that preoperative Imatinib was associated with improved surgical margins while perioperative Imatinib resulted in improved disease free and overall survival in rectal GISTs (Jakob et al., 2013). A study from India demonstrated the role of Imatinib in adjuvant and therapeutic settings and reported that responses were durable and most patients tolerated the drug well at clinically effective doses (Kapoor et al., 2013). Newer drugs, such as sunitinib are also coming up and may be effective in patients who become resistant to gleevec. A study by Li et al. on Chinese patients with gleevec resistant or intolerant GISTs showed that Sunitinib was effective in such patients and they tolerated this drug well (Li et al., 2012). Similar findings were reported by Yoon et al in Korean patients (Yoon et al., 2012). In turn, even newer drugs which may be useful in patients with advanced tumors and resistance to both imatinib and sunitinib are also coming up fast (DeMatteo et al., 2009; Blay et al., 2010; Demetri et al., 2013; Joensuu et al., 2013). Recently, a study from China demonstrated that surgical removal of metastatic lesions of GISTs in patients who were also receiving and responding to Imatinib improved the outcome in such patients (Du et al., 2014). Thus the role of surgery in patients with recurrent or metastatic GISTs who were responding to Imatinib is currently a subject for additional research.

A study by Sevinc et al. investigated cyclooxygenase 2 (COX-2) expression in GIST. Their findings demonstrated that use of Cox-2 inhibitors, with or without Tyrosine Kinase inhibitors, may be helpful in the adjuvant setting in preventing or delaying recurrence (Sevinc et al., 2010).

Follow up was available in 95 cases out of which 69 patients are alive and 26 patients died. A glance at table 6 shows that most of these patients, irrespective of location, had high risk tumors. Most of these patients lived on average a few months to one to two years after initial surgical resection. Only one patient, with an intermediate risk tumor in the jejunum, survived for 6 years after resection. It appears that at least for most of these 26 patients who died, Gleevec status apparently did not significantly alter the clinical course. However, in a poor country like Pakistan, where compliance issues are very important, it is quite possible that poor response to Gleevec may in reality represent lack of compliance rather than failure of response to the drug. Of the 69 patients who are alive, the majority have high risk tumors irrespective of the location. Most of these patients had resections in the last four to five years (Table 7). As shown in Table 7, 3 patients with small intestinal GISTs, one with a low risk and two with intermediate risk tumors, have survived since their

initial resection in 2005 and 2006. Conversely, 4 patients with high risk gastric GISTs who were initially operated in 2010 and later have developed early metastatic disease. As most of the 69 patients who are alive underwent initial resection relatively recently i.e. over the last four to five years (many as late as 2013), it may be too early yet to assess the impact of Gleevec therapy on the clinical course of these patients. A study from India showed that preoperative Gleevec resulted in enough downstaging in patients with locally advanced GIST allowing resection with negative margins in a fairly good proportion of such patients (Ashraf et al., 2011). Similarly, a recent study from Taiwan demonstrated that the outcome for patients with GIST has improved significantly with the availability and wider use of Gleevec (Chiang et al., 2014).

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