

**Management of gastrointestinal stromal tumors: Five years period, Tanta experience**Mohamed El-Shebiny<sup>1</sup>, Alaa Maria<sup>1</sup> and Emad Sadaka<sup>1</sup> and Ayman El-Namer<sup>2</sup><sup>1</sup>Clinical Oncology department, Faculty of Medicine, Tanta University, Egypt<sup>2</sup>General Surgery department, Faculty of Medicine, Tanta University, Egypt  
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**Abstract: Background:** Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasm of the gastrointestinal (GI) tract. Surgical resection has remained the mainstay of treatment of GISTs with a 5-year survival of 29–35%. Gastrointestinal stromal tumors have only been described based on their specific immunohistochemistry and the presence of particular KIT-related mutations which potentially make them targets for tyrosine kinase inhibition. We present our experience of managing GISTs, 5-years period. **Methods:** We reviewed clinical, pathological records and treatment outcome of 22 patients (14 men and 8 women) with GISTs treated at General Surgical and Clinical Oncology Departments, Tanta University Hospital during the period from Jan 2007 to Dec 2011. **Results:** The stomach was the most common site of origin (45.45%). The mean tumor diameter was 7±3.1 (range 4–18) cm. We detected advanced-stage tumors in 18.18% of patients. Complete resection was performed in 77.27% of patients. Mitotic count was greater than 5 high-power field (HPF) in 31.82 % patients. Immunohistochemical staining for CD117 was positive in 90.91% patients. The mean follow-up period was 26.7±15.1 (range 7–55) months. Distant metastases developed in 18.18% of all patients within an average of 14.5 (range 7–21) months. Local recurrence had occurred in 29.41% of patients who underwent complete surgical resection within an average of 11.4 (range 4–18) months. Imatinib mesylate therapy was administered for 11 patients (4 patients had positive margins, 3 patients had locally recurrent disease and 4 patients had distant metastases) with a median survival of 21 (range 7-37) months. The median length of survival for all patients was 29 months and the 3-year overall survival (OS) and disease free survival (DFS) rates were 54.55% and 45.45% respectively. Three-year OS rates were 58.82 % versus 40% for patients who underwent complete surgical excision versus those who underwent incomplete surgical excision respectively ( $p=0.61$ ). The 3-year OS rates were 76.92% versus 22.22% for low & intermediate versus high malignant risk patients respectively ( $p=0.008$ ). **Conclusion:** Treatment of GISTs should be made on an individual basis. Surgical resection is considered the gold standard therapy for resectable GISTs and the completeness of the resection with negative margins is the main goal of surgery. Large multi-centers studies with large number of patients are needed for further insight into issues of tyrosine kinase inhibitors dosage, treatment duration and the selection, timing and monitoring of further therapeutic interventions.

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**Key words:** Gastrointestinal stromal tumors, c-KIT protein, Imatinib mesylate.

**1. Introduction**

Gastrointestinal stromal tumors (GISTs) are rare neoplasm that account for 0.1%–3% of all GI tract tumors with an incidence of 10–20 cases per million.<sup>(1-4)</sup>

These tumors arise from the Cajal's interstitial cells located in mesodermal tissue and were defined as primary mesenchymal tumors. Diagnosis requires immunohistochemical staining for the expression of c-KIT protein.<sup>(5, 6)</sup>

GISTs occur predominantly in people over the age of 40 years, with a small male predominance.<sup>(4, 7, 8)</sup> They may or may not cause symptoms, depending on their location, and they are often discovered incidentally. The stomach is the most common site of involvement, followed by the small intestine, colon, rectum and esophagus.<sup>(4, 6, 9-11)</sup>

Surgical resection is currently the “gold standard” in the management of GISTs. Complete resection with negative margins is the main goal of surgery. Nevertheless, the survival rate in patients with GISTs is low, whereas the rates of local recurrence or metastases are high.<sup>(12)</sup> Imatinib mesylate has been proven to be highly efficacious for the treatment of advanced/metastatic GISTs.<sup>(13-15)</sup> Moreover, imatinib mesylate is not recommended as adjuvant therapy in patients who have complete resections unless a recurrence is observed.<sup>(16, 17)</sup> Radiotherapy and conventional chemotherapy are known to be ineffective in the management of GISTs.<sup>(18, 19)</sup>

Overall survival after surgical resection and clinical behavior are depending on tumor size and mitotic count, regardless their benign or malignant microscopic features.<sup>(20)</sup> The disease-specific 5-year

survival rate for patients with malignant GISTs is 29%–35 %.<sup>(9, 21, 22)</sup>

## 2. Material and Methods

This is a retrospective study included 22 patients with GISTs treated at General Surgical and Clinical Oncology Departments, Tanta University Hospital throughout the period from Jan 2007 to Dec 2011.

### Eligibility criteria

All studied patients were an Eastern Cooperative Oncology Group (ECOG) performance status score <2 with a histologic diagnosis of primary GISTs expressing Kit protein by immunohistochemistry, adequate liver, renal and blood tests.

The patients' age, gender, presenting clinical symptoms, tumor site, maximal tumor diameter after resection, surgical procedure, extent of surgical resection, the presence and date of local recurrence or distant metastases, and the clinical outcome until last follow-up, including date of death were recorded. After the treatment, patients were followed regularly using history, physical examination, chest x-ray, and abdominopelvic computerized tomography (CT) scan. The follow up protocol had carried out every 3-6 months for 3 years then annually.

During the preoperative period, we obtained biopsy specimens by endoscopic interventions, which helped the diagnosis of GISTs after careful histopathologic evaluations. The purpose of surgery was to resect the tumor completely, including invaded adjacent tissues. We considered resection to be complete if margins of the resected material were clear (R0), whereas we considered the procedure to be incomplete if positive margins were detected.

Imatinib mesylate therapy with a dose of 400 mg/day was administered orally after surgery in patients with 1) incomplete tumor resection, 2) recurrent tumor after complete resection and 3) metastatic disease.

### Immunohistochemistry

Tumors samples from 20 patients were defined as GISTs after they displayed c-kit (CD117) immunopositivity. Additional immunohistochemistry studies to corroborate the diagnosis such as CD34 were performed for 18 patients.

Patients were classified according to risk and their potential for aggressive clinical behavior based on the National Institutes of Health consensus statement of 2001 for GISTs (Fletcher's classification)<sup>(6)</sup> (Table 1).

### Statistics

Statistical analysis was performed with the Statistical Package for the Social Science (SPSS, Chicago, IL USA) software package, V-12. Overall

survival was calculated from the day of diagnosis until death or the last day of a patient's visit to the outpatient clinic. Disease-free survival rate was calculated from the first diagnosis until tumor recurrence or distant metastases were found. Kaplan-Meier analysis with a log-rank test was used to compare survival rates.<sup>(23)</sup>

## 3. Results

Throughout the period from Jan 2007 to Dec 2011, 22 patients with available data were treated for GISTs at General Surgical and Clinical Oncology departments, Tanta University Hospital. The clinical characteristics of all patients, by tumor locations are summarized in Table (2). Mean age was 60.1±8 (range 44–78) years and prevalence of the disease was higher in males (63.64%) with a male to female ratio was 1.75: 1. Tumors were most commonly located in the stomach (45.45%), followed by the small intestines (31.82%), colon (18.18%), rectum (4.54%) and we found no GISTs in the esophagus. Abdominal pain represented the most common clinical presentation (63.64%), followed by weight loss (27.27%), fatigue, dyspepsia and anemia (22.73%). Immunohistochemical staining for CD117 was positive in 20 (90.91%) patients and CD34 was positive in 11 (50%) patients.

**Table (1): Proposed classification of GISTs by relative risk of malignancy.<sup>(6)</sup>**

Risk	Tumor size	Mitotic count / HPF
Very low risk	<2 cm	<5/50 HPF
Low risk	2-5 cm	<5/50 HPF
Intermediate risk	<5 cm	6-10/50 HPF
	5-10 cm	<5/50 HPF
High risk	>5 cm	>5/50 HPF
	>10 cm	Any mitotic rate
	Any size	>10/50 HPF

HPF: High power field

Advanced-stage tumors were detected in 4 (18.18%) patients; of these 3 (13.64%) had locally advanced tumors and metastatic disease was represented in only one (4.55%) patient to the liver.

Methods for diagnosis had done to the studied patients, included plain radiography (100%), double-contrast radiographic investigations (59.09%), pelviabdominal ultrasonography (100%), computed tomography (100%), magnetic resonance imaging (36.36%), gastroduodenoscopy (63.64%), colonoscopy and rectosigmoidoscopy (54.55%). Endoscopic biopsy specimens were obtained in the preoperative period for 10 patients with stomach and colorectal tumors (45.45%), but not from those who had tumors in the small intestine. Of the 10 patients from whom endoscopic specimens were obtained, 6 (60%) patients had received a diagnosis of GIST after the biopsy. The remaining studied patients had diagnosed with post-operative specimen for immunohistochemical studies.

Table (3) shows surgical procedure that was performed. Complete resection was achieved in 17 (77.27%) patients. Laparoscopic surgery was not done for any patients. Three patients (13.64%) underwent emergency surgeries owing to obstruction (9.09%), and GI system hemorrhage (4.55%). Five patients experienced postoperative complications: wound

infection in 13.64%, anastomosis failure and hemorrhage in 4.55% for both. Patient with anastomosis failure had received total gastrectomy plus splenectomy owing to a tumor in the stomach. One patient experienced hemorrhage due Whipple procedure required re-exploration.

**Table (2): Clinical characteristics of 22 patients with GISTs, by tumor location.**

Characteristic	Tumor location; no. (%)				
	All patients 22 (100)	Stomach 10 (45.45)	SI 7 (31.82)	Colorectal 5 (22.73)	
Age~	≤ 60 years	11 (50.00)	4 (36.36)	4 (36.36)	3 (27.27)
	> 60 years	11 (50.00)	6 (54.55)	3 (27.27)	2 (18.18)
Sex	Female	8 (36.36)	4 (50)	4 (50)	0 (0.00)
	Male	14 (63.64)	6 (42.86)	3 (21.43)	5 (35.71)
Main symptom	Abdominal pain	14 (63.64)	6 (42.86)	4 (28.57)	4 (28.57)
	Weight loss	6 (27.27)	4 (66.67)	1 (16.67)	1 (16.67)
	Dyspepsia	5 (22.73)	5 (100)	0 (0)	0 (0)
	Anemia	5 (22.73)	2 (40)	2 (40)	1 (20)
	Fatigue	5 (22.73)	3 (60)	1 (20)	1 (20)
	Nausea and vomiting	4 (18.18)	3 (75)	1 (25)	0 (0)
	Constipation	3 (13.64)	0 (0)	1 (33.33)	2 (66.67)
	Diarrhea	3 (13.64)	0 (0)	3 (100)	0 (0)
Immunohistochemical findings	GI hemorrhage	3 (13.64)	2 (66.67)	1 (33.33)	0 (0)
	CD117 +ve	20 (90.91)	10 (50)	5 (25)	5 (25)
	CD117 -ve	2 (9.09)	0 (0)	2 (100)	0 (0)
	CD34 +ve	11 (50)	7 (63.64)	2 (18.18)	2 (18.18)
	CD34 -ve	7 (31.82)	2 (28.57)	4 (57.14)	1 (14.29)
Local invasion/metastases	CD34 Unknown	4 (18.18)	1 (25)	1 (25)	2 (50)
	No	18 (81.82)	8 (44.44)	6 (33.33)	4 (22.22)
	Yes	4 (18.18)	2 (50)	1 (25)	1 (25)

~ Mean 60.1±8 (range 44–78) years; SI, Small intestine.

Malignant risks based on tumor location are listed in Table (4). The mean tumor diameter was 7±3.1 (range 4–18) cm. The mean mitotic count was 5.8 (SD±4.9, range 2–19) HPF. We detected mitoses less than 5/50 HPF in 15 (68.18%) patients and mitoses equal to or greater than 5/50 HPF in 7 (31.82%) patients. Using Fletcher's classification; out of 22 patients, 9 (40.91%) patients were high risk, 9 (40.91%) patients were intermediate risk and 4 (18.18%) patients were low risk.

**Table (3): Surgical procedures performed in 22 patients with GISTs, by tumor location.**

Surgical procedure	Tumor location		
	All patients 22 (100)	Complete 17 (77.27)	Incomplete 5 (22.73)
<b>Stomach</b>	<b>10 (45.45)</b>	<b>7 (70)</b>	<b>3 (30)</b>
Total gastrectomy + splenectomy	3 (30)	3 (100)	0 (0.0)
Distal subtotal gastrectomy	5 (50)	3 (60)	2 (40)
Gastric wedge resection	2 (20)	1 (50)	1 (50)
<b>Small intestine</b>	<b>7 (31.82)</b>	<b>6 (85.71)</b>	<b>1 (14.29)</b>
Partial resection	6 (85.71)	5 (83.33)	1 (16.67)
Whipple procedure	1 (14.29)	1 (100)	0 (0.00)
<b>Colon and rectum</b>	<b>5 (22.73)</b>	<b>4 (80)</b>	<b>1 (20)</b>
Abdominoperineal resection	1 (20)	1 (100)	0 (0.00)
Left hemicolectomy	3 (60)	2 (66.67)	1 (33.33)
Right hemicolectomy	1 (20)	1 (100)	0 (0.00)

**Table (4): Malignant risk classification in 22 patients with GISTs, by tumor location.**

Finding	Tumor location; no. (%)			
	All patients 22 (100)	Stomach 10 (45.45)	SI 7 (31.82)	Colorectal 5 (22.73)
<b>Tumor diameter</b>				
≤5 cm	6 (27.27)	5 (83.33)	1 (16.67)	0 (0.00)
5.1–10 cm	14 (63.64)	4 (28.58)	5 (35.71)	5 (35.71)
> 10 cm	2 (9.09)	1 (50)	1 (50)	0 (0.00)
<b>Mitosis count</b>				
< 5/50 HPF	15 (68.18)	7 (46.67)	6 (40)	2 (13.33)
5–10/50 HPF	3 (13.64)	0 (0.00)	1 (33.33)	2 (66.67)
> 10/50 HPF	4 (18.18)	3 (75)	0 (0.00)	1 (25)
<b>Fletcher's classification</b>				
Low	4 (18.18)	3 (75)	1 (25)	0 (0.00)
intermediate	9 (40.91)	3 (33.33)	4 (44.45)	2 (22.22)
High	9 (40.91)	4 (44.45)	2 (22.22)	3 (33.33)

SI: Small intestine; HPF: High power field.

Out of 17 patients who underwent complete surgical resection, we detected local recurrence in 5 (29.41%) patients (3 out of 9 patients with high-risk tumors and 2 out of 9 patients with intermediate-risk tumors with no local recurrence was detected in any of the 4 patients with low-risk tumors) within an average of 11.4 (range 4–18) months. Re-excision of the recurrent tumors had done in 2 of 5 patients (40%) and the other three patients had received tyrosine kinase receptor inhibitor (imatinib mesylate).

Four out of five patients underwent incomplete surgical resection were treated with imatinib mesylate

therapy: two patient developed a local disease progression after 15 and 17 months that required a second surgical intervention followed by continued therapy with imatinib mesylate therapy (no second line tyrosine kinase inhibitors were available) and 2 patients were free from disease at 32 and 40 months.

Distant metastases developed in 4 patients (18.18%), the primary tumor was a high risk rectal and small intestine GISTs (2 patients) with liver metastases and a stomach GISTs (2 patients) with peritoneal metastases) within an average of 14.5 (range 7–21) months. All patients with distant metastases received

imatinib mesylate therapy and none of them underwent repeat surgery.

The mean follow-up period was  $29 \pm 14.9$  (range 5–55) months with a median survival time was 29 months. The 3-year OS rate was 54.55% and DFS rate was 45.45%, Figures (1& 2).

Figure (3) shows the OS rates according to completeness of excision in 22 patients with GISTs. Three-year OS rates were 58.82% versus 40% for patients who underwent complete surgical excision versus those who underwent incomplete surgical excision respectively ( $p=0.61$ ).

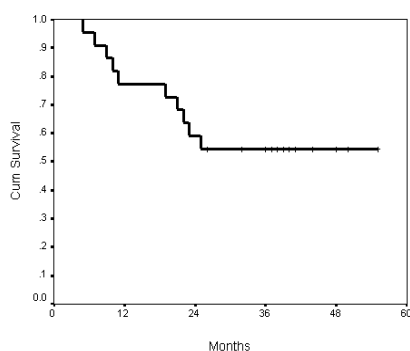


Figure (1): Overall survival rate in 22 patients with GISTs.

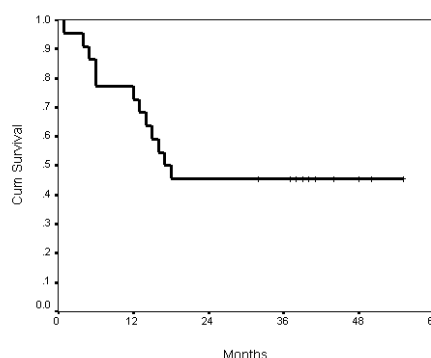


Figure (2): Disease free survival rate in 22 patients with GISTs.

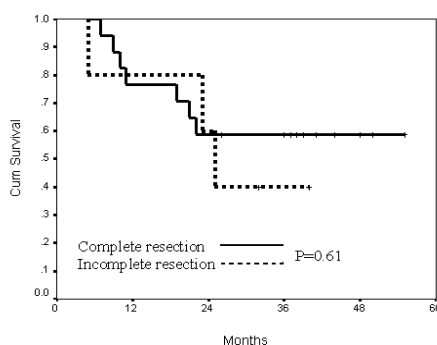


Figure (3): Kaplan Meier survival curves showing OS by completeness of excision.

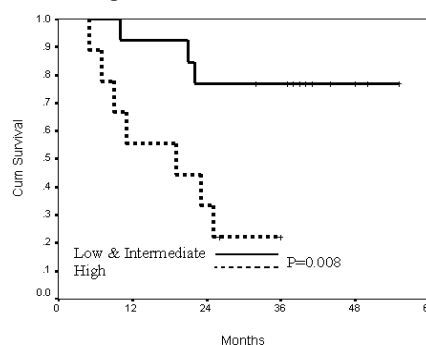


Figure (4): Kaplan Meier survival curves showing OS according to malignant risk groups.

Figure (4) shows the OS rates according to malignant risk groups (low & intermediate versus high risk) in 22 patients with GISTs. Three-year OS rates were 76.92% versus 22.22% for low & intermediate versus high malignant risk patients respectively ( $p=0.008$ ).

#### 4. Discussion

During five years period of the present study, GISTs constituted about 1.6% of all GI tumors presented at Tanta University Hospital. Rossi *et al.*<sup>(2)</sup> reported that GISTs make up 0.1%–3% of all GIT tumors and 5% of all soft-tissue sarcomas.

In our study mean age of patients was  $60.1 \pm 8$  (range 44–78) years and none of patients presented in the childhood period. DeMatteo *et al.* and Nilsson *et al.*<sup>(21, 24)</sup> reported that GISTs occur most commonly in adults, with a median age at diagnosis of 60 years (range 40–80). Miettinen & Lasota<sup>(25)</sup> had found that, these tumors may be observed in children, often as a familial syndrome.

In many series GISTs were most commonly located in the stomach (39%–70%) and small intestine (20%–35%), whereas the colon and rectum (5%–12%) and esophagus (2%–5%) were less common locations.<sup>(3, 5, 11, 26, 27)</sup> Consistently, we found in our

study that GISTs were located most commonly in the stomach (45.45%), followed by the small intestine (31.82%).

Gastrointestinal stromal tumors may not cause symptoms; they may cause nonspecific symptoms depending on the location of the tumor and they may be detected incidentally during investigation of these symptoms or during autopsy.<sup>(28, 29)</sup> Abdominal pain, melena and weight loss are the most common symptoms in patients with GISTs.<sup>(30)</sup> Rarely, an abdominal mass is palpable. In a population-based study conducted with Nilsson *et al.*<sup>(24)</sup> of 288 primary GISTs, 69% of tumors were symptomatic, 21% were discovered incidentally at surgery, and 10% were discovered at autopsy. Small GISTs (<2 cm) may be asymptomatic, detected incidentally on radiographic studies, endoscopy, or laparotomy. The most common symptoms in our patients were abdominal pain (63.64%), weight loss (27.27%), fatigue, anemia and dyspepsia (22.73%) for each.

Definitive diagnosis can be established after histopathologic investigations. A “full-layer biopsy” should be obtained by an experienced endoscopist for true histopathologic diagnosis, because GISTs have submucosal localization. For this reason, some authors reported that GISTs had been diagnosed in only 27%–50% of the cases by endoscopic biopsy.<sup>(16, 31)</sup> In our study, endoscopic biopsies were obtained from 45.45% of the patients, and GISTs were diagnosed in 60% of the biopsy specimens in the preoperative period.

The literature concerning surgical resection in patients with primary GISTs has several limitations. Most reports discuss few patients because the disease is uncommon. Essentially, most studies are retrospective and span a long period (e.g. 20-30 years). Most results are also confounded by the inclusion of patients with other GI sarcomas because of the previous inconsistency in the definition.<sup>(32)</sup>

Surgery represents the gold standard treatment for respectable GISTs. Principles of a correct procedure include negative margins on the specimen and integrity of the pseudocapsule.<sup>(33)</sup> Gastrointestinal stromal tumors do not metastasize through lymphatic spread, so systematic lymphadenectomy is not indicated. Survival at 5 years after surgical resection is extremely variable in the reported series, ranging from 30%–65%.<sup>(5, 20, 21, 34, 35)</sup> This variability could be explained by the amount of knowledge of the disease and, most of all, by the introduction of the inhibitors of tyrosine kinases.<sup>(36)</sup> In the present study, we observed a 3-year OS and DFS rates of 54.55% and 45.45 % respectively (Figs. 1& 2)

Completeness of resection is an important factor that affects survival in patients with GISTs. In the present study the 3-year OS rates were 58.82% versus 40% for patients who underwent complete surgical resection versus those who had positive

margins ( $p=0.61$ , Fig. 3). We found a median survival rate of 28 months and 24 months in patients who had complete resections with and without negative margins, respectively. Many authors had reported a 5-year OS rate ranging from 32% to 93% following complete surgical resection.<sup>(20, 21, 34, 37, 38)</sup> The effects of incomplete resection on survival rates among patients with advanced-stage GISTs are controversial. According to Wu *et al.*<sup>(39)</sup> debulking of large tumors could increase the effectiveness of chemotherapy even if negative margin was not maintained. On the contrary, Langer *et al.*<sup>(40)</sup> concluded that incomplete resection only helped patients recover from symptoms as pain or hemorrhage and that did not affect survival. Crosby *et al.*<sup>(8)</sup> and DeMatteo *et al.*<sup>(21)</sup> reported 5-year OS rates after incomplete resection of 8% and 9%, respectively.

In the present study the 3-year OS rates for patients presented with tumors <5 cm versus patients presented with tumors  $\geq 5$  cm were 66.67% versus 50% respectively ( $p=0.43$ ). Fletcher *et al.* and DeMatteo *et al.* had reported that, longer survival has been reported for tumors smaller than 5 cm in diameter.<sup>(6, 21)</sup>

With a simple histopathologic approach, a given tumor can be considered malignant when a mitotic count greater than 5/50 HPF is detected.<sup>(16)</sup> In our study, tumors in 31.82% of patients had a mitotic count greater than 5/50 HPF and the 3-year OS rate was 14.29%. Pithorecky *et al.*, DeMatteo *et al.*, and Pierie *et al.* had reported that, regardless of presentation, the 5-year OS rate for patients with malignant GISTs is ranging from 29% to 35%.<sup>(9, 21, 22)</sup>

The relation between the location of the tumor and the patient's survival is controversial. DeMatteo *et al.*<sup>(21)</sup> proposed that the patient's survival depended on the location of the tumor, whereas Lillemoie & Efron<sup>(41)</sup> suggested the opposite. There is consensus, however, on fair prognosis of GISTs located in the stomach.<sup>(5, 6, 20, 37)</sup>

Radiotherapy and conventional chemotherapy are known to be ineffective in the management of GISTs.<sup>(18, 19)</sup> Imatinib mesylate was first used as medical therapy for GIST in 2000.<sup>(42)</sup> Several clinical trials later confirmed that imatinib mesylate was safe and effective in the treatment of advanced and metastatic GISTs.<sup>(13, 43, 44)</sup>

Consistent with the report by Kubota<sup>(17)</sup>, imatinib mesylate was administered to patients with 1) incomplete tumor resection, 2) unresectable recurrent tumor or failure to perform repeat surgery for complete resection of the recurrent tumor and 3) unresectable metastatic disease. In this study imatinib mesylate therapy was administered for 11 patients (4 patients had positive margins, 3 patients had locally recurrent disease and 4 patients had distant metastases) with a median survival of 21 (range 7-37) months. However,



our small sample does not allow us to comment on the statistical significance of the long-term consequences of this treatment.

Two phase II trials had tested imatinib mesylate as a neoadjuvant therapy for GISTs and concluded that the survival benefit imatinib and the decision to use neoadjuvant imatinib should be individualized.<sup>(45,46)</sup>

Although, imatinib mesylate was not recommended as adjuvant therapy in patients who have complete resections unless a recurrence is observed, in 2009 the American College of Surgeons Oncology Group presented the results of a randomised Phase III Multicenter Trial that showed the effectiveness of imatinib mesylate as adjuvant therapy for primary GISTs in term of recurrence free and OS.<sup>(47)</sup>

Imatinib mesylate was first approved in 2002 for use in advanced GIST in a phase II study of 147 patients with an overall objective response rates of 53.7% with very manageable toxicities.<sup>(13)</sup> This represented a remarkable advancement in therapy for patients with metastatic GIST. With longer follow-up, these results continue to hold true. Overall median time to progression being 24 months and median OS reported as 57 months. Overall survival was not different in patients who achieved an objective response or stable disease.<sup>(14)</sup>

Recurrence is one of the most important problems among patients with GISTs even if complete resection has been performed. DeMatteo *et al.*<sup>(21)</sup> and Pierie *et al.*<sup>(22)</sup> reported recurrence rates of about 40%–52%. In the present study local recurrence had occurred in 29.41% of patients who underwent complete surgical resection within an average of 11.8 (range 4–17) months. Distant metastases developed in 18.18% of patients within an average of 10 (range 5–15) months. Tumors re-excision in a repeat surgery had done in 40% of patients with local recurrence, whereas patients with distant metastases did not undergo repeat surgery. The median survival was 20.6 and 14.8 for recurrent and metastatic patients respectively.

On the other hand, DeMatteo *et al.*,<sup>(21)</sup> Shawver *et al.*<sup>(48)</sup> and Roberts & Eisenberg<sup>(49)</sup> had reported that, the median survival in patients with local recurrence was shorter compared with those with metastatic disease. Thus, complete resection of recurrent tumors would affect survival in a positive way. However, surgical intervention bears a high risk of morbidity and mortality in these patients.

*In conclusion*, treatment of GISTs should be made on an individual basis. Surgical resection is considered the gold standard therapy for resectable GISTs and the completeness of the resection with negative margins is the main goal of surgery. Large multi-centers studies with large number of patients are needed for further insight into issues of tyrosine kinase inhibitors dosage,

treatment duration and the selection, timing and monitoring of further therapeutic interventions.

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