

Clinical trends and surgical outcome in management of gastrointestinal stromal tumors

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Ref: 6-278-2012

Coming: 14-3-2012

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Abstract

Background: Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. Our aim in this study is to find out clinical evaluation and surgical outcome in management of these types of tumors.

Patients and methods: 11 consecutive patients subjected to surgical treatment, diagnosed histopathologically as GISTs and enrolled in a prospective study from October 2007 to March 2011.

Results: 7 gastric and 4 small intestinal GISTs presented mainly by Gastrointestinal bleeding (36%) and abdominal pain (36%). 6 cases (55%) were discovered incidentally during laparotomy. All patients were managed surgically and confirmed by postoperative histopathologic study. Surgical resection with safety margin was done to all patients except one case with duodenal GIST was irresectable.

5 patients with poor prognostic factors and inoperable lesions required a second therapy in Oncology Unit. During the follow up period (ranged from 6-34months) 2 patients died due to progression of the disease and distant metastasis.

Conclusion: GISTs are commonly diagnosed incidentally during laparotomy and most of them presented with gastrointestinal bleeding and abdominal pain .Complete surgical resection is the mainstay of their management. Urgent cases of GISTs carry poor prognosis, but further clinical trials are needed to establish this factor.

Keywords: GIST; Gastrointestinal tumors; Management outcome.

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract¹. Historically, these were classified as leiomyomas or leiomyosarcomas because they possessed smooth muscle features when examined under light microscopy². Since the term GIST was introduced by Mazur and Clark in 1983, who demonstrated that GISTs do not arise from smooth muscle cells, but from another mesenchymal derivative such as the progenitors of spindle and epithelioid cells³.

GISTs are usually kit positive, that are believed to originate from interstitial cell of Cajal, the gut pace maker of the autonomic nervous gut system, or their related stem cells^{4, 5}. The incidence of GISTs in the United States is estimated to be 3000-4000 cases per year⁶, with the age of majority of the diagnosed patients being in the range of 40-80 and a median age of 60 years⁷.

GISTs may develop through the entire gastrointestinal tract: 50-70 % in the stomach, 25-30% in the small intestine, 5-10% in colon and rectum, < 5% in the oesophagus, the remaining may arise within the omentum or within the peritoneal layers and termed extra-gastrointestinal stromal tumors (EGISTs)⁸.

The most common clinical presentation of these tumors is gastrointestinal bleeding (with acute hematemesis, melana, or chronic anaemia), they may cause GI obstruction, abdominal pain, weight loss or a palpable mass, otherwise they can be incidentally detected during surgery or endoscopic / radiological procedures⁹⁻¹².

The strategy of GIST treatment is based on two gold standards: surgery and target molecular therapy¹³. Localized GIST has historically been treated with combination of surgery and chemotherapy; however, because chemotherapy has been proven ineffective in the treatment of GIST, surgical resection is now the primary treatment for respectable tumors¹⁴.

The aim of surgical treatment is complete resection, avoiding tumor rupture, preferring wedge resection when ever possible; lymphadenectomy is not recommended due to the rarity of nodal metastasis¹⁵. Although surgical resection is currently the standard¹⁶, complete gross resection of localized GIST is associated with a 5- year survival of 48-65%¹⁷⁻¹⁹. Poor survival is mainly associated with high recurrence rates which are >40% within the first 2 years following surgical resection¹⁸.

Prognosis is related to the size of the tumor and to the mitotic rate: tumors >10 cm or with a mitotic rate > 5 per 50high- powered fields (HPF) have a higher risk of recurrence and metastasis. Other prognostic factors are tumor location, persistence of tumor residuals within the surgical resection margins, tumor rupture, and c-kit mutation that may interfere with efficacy of target molecular therapy.⁹⁻¹² Neoadjuvant target molecular therapy can be considered for patients with inoperable GISTs (unresectable ,metastatic or recurrent tumors) or for downsizing the tumor before surgical resection.¹

The majority of GISTs with kit –mutant proteins are sensitive to agents that block kit and platelet-derived growth factor receptor (PDGFR), with a response rate that reaches almost 70% even in advanced disease²⁰; however resistance to the therapy has been widely reported²¹.

The primary aim of this study is to find out the clinical evaluation and the surgical outcome in management of GIST patients.

Patients and Methods

This retrospective observational study was carried out in Surgery Department at Sohag University Hospital from October 2007-to March2011. All eligible cases had consented. Patients in this study included 11 cases diagnosed histopathologically as GIST and subjected to surgical treatment whether operable or inoperable. They were diagnosed preoperatively via endoscopic biopsy or discovered incidentally during laparotomy.

Our patients were subjected to: complete clinical evaluation; abdominal ultrasound, CT abdomen and pelvis, endoscopy was used in some cases. Routinely postoperative block histopathological biopsy was recommended to assess the extent of safety margin and the grade of mitotic index.

As a rule, surgical treatment was recommended for all resectable tumors. Our goal in the surgical management of primary respectable GISTs was complete resection with safety margin. Excision of the tumor with negative resection margin is termed (R₀), R₁ (Persistence of microscopic tumor deposits within the resection margin) and R₂ (persistence of macroscopic tumor residual)²².

Postoperatively, patients with poor prognostic factors and inoperable cases (distant metastasis, peritoneal deposits, recurrent and irresectable tumors) were referred to Oncology Unit for target molecular therapy (imatinib mesylate)

Clinical evaluation and follow up was done to all patients every 3 month during the first year and each 6 months later on in a regular outpatient visits. The patients were evaluated clinically and by imaging studies via abdominal ultrasound and CT.

Results

This prospective study included 11 patients with GIST, 7 males (64%) and 4 females (36%), their ages ranged from 32-73 years with mean of 51 ± 4 .

The definite preoperative diagnosis was detected only in 5 patients (45%) with gastric GIST where they were evaluated clinically, CT abdomen and confirmed by endoscopic biopsy; the other 6 cases were discovered incidentally during laparotomy due to abdominal pain (3 cases), gastrointestinal obstruction (2 cases) and abdominal mass in the last case.

Tumor's localization (table1, Fig1,2,3):

It was found that 7 patients had gastric GIST, 2 cases in the jejunum, 1 in the ileum and the last patient in the duodenum.

Symptoms and clinical presentation (table2):

The symptoms were variable according to location of the lesion. The most common symptom were GI bleeding, abdominal pain, gastrointestinal obstruction and a palpable mass.

Operative findings (table3, Fig, 4, 5):

Elective surgical interference was done to all cases except in 2 patients; one with intestinal obstruction (jejunal GIST) and the other with acute abdomen that was misdiagnosed as acute appendicitis (ileal GIST).

Primary resection was done to all patients except in one case with duodenal GIST that was fixed to the posterior abdominal wall and associated with peritoneal deposits (Gastrojejunostomy was done to bypass the obstruction and biopsy was taken).

Preoperative imaging studies and intraoperative clinical assessment proved the presence of distant metastasis in 3 cases (2 with liver metastasis and one with peritoneal deposits).

Histopathologic study (table3):

Successful primary resection with safety margin (Ro) was found in 8 cases, while 2 cases showed persistence of microscopic tumor deposits (R1) and the remaining one was irresectable.

The mitotic index was $<5/50$ HPF in 6 cases; ranged from 5-10/50 HPF in 3 specimens and $>10/50$ HPF in 2 cases.

The diameter of the studied resectable GISTs was found in gastric series ranged from 3-11cm with a mean 6.4 cm ; in jejunal GIST ranged from 6-7.5 (mean is 6.8 cm) , in illeal GIST 3.5 cm and the duodenal type was irresectable.

Follow up and outcome (table 4):

Last update of follow up has been reported on September 2011. Two patients were lost to follow up, while the remaining 9 cases were followed up with a mean 22 months (range 6-34 months).

During the first month after operation , the early postoperative complications occurred in 4 patients, which included wound infection in 2 patients, wound dehiscence in 1 case and the last one developed prolonged ileus ; all of them improved by conservative measures. Late postoperative morbidity occurred in 2 cases with gastric GISTs that

developed local recurrence, 8 and 10 months respectively after surgery, the first one died due to progression of the disease with distant metastasis.

Five patients (with unresectable, metastatic and recurrent tumors) required a second therapy in Oncology Unit Department during their follow up period.

Two out of 9 cases that were followed up died 7 and 10 months postoperatively, the first one showed irresectable duodenal GIST with peritoneal deposits, while the other with large gastric GIST (11cm in diameter) showed local recurrence and liver metastasis. The cause of death in both cases was due to disease progression and distant metastasis.

Discussion

GIST is the most common mesenchymal tumor of the gastrointestinal tract. Surgery with complete removal of the tumor is the primary treatment for resectable GIST and the only chance of cure. However, recurrence after surgery is common ¹.

GISTs usually affect both sexes equally²², however we reported a mild prevalence of males, with a male: female rate of 1.75. Preoperative histological diagnosis is very uncommon; Horowitz 1995 ²³ reported 50% of success rate, higher if obtained with ultrasound endoscopy, however percutaneous biopsy is not recommended due to high dissemination risk.

In this literature, the definite preoperative histological diagnosis was detected in 5 patients with gastric GIST, only 45% via diagnostic upper endoscopic biopsy and the remaining cases diagnosed incidentally due to different aetiological findings that necessitating laparotomy.

Gastrointestinal bleeding and abdominal pain were the commonest symptoms in our series and this is in agreement with many other studies ²⁴⁻³⁰.

In this study, it is noticed that the 4 cases with small intestinal GIST, 2 of them (50%) had acute symptoms and underwent urgent laparotomy and this is consistent with other studies which stated that small intestinal GIST usually discovered incidentally during urgent laparotomy ²⁸⁻³¹.

During the follow up period (ranged from 6-34 months) 2 patients were lost to follow up, while the remaining cases (9 patients), 2 of them (22%) died in the postoperative 7 and 10 months respectively due to progression of the disease and distant metastasis. These 2 cases presented with acute symptoms (acute abdominal pain and massive upper gastrointestinal bleeding), while the remaining cases especially those with

elective surgical resection showed good postoperative outcome and this is consistent with the study of Salvator et al; 2011²² who concluded that patients presented with acute abdomen reported a worse survival rate if compared with other presentations, but the symptoms can not be considered per se predictive of survival and outcome. They added that patients presenting with acute abdomen were those more likely to have more than one, unfavorable prognostic factor.

The mortality rate in our study is 22%; it is fairly considered to be acceptable as compared with other many studies that reported the 5 year survival rate is (48-65%)¹⁷⁻¹⁹ after complete gross resection of localized GIST, considering our recorded results performed in a small number of investigated cases and during less follow up period.

This variation in the results of the surgical outcome may be due to the difference in patient selection criteria, tumor size and location, extent of mitotic activity, in addition to the facilities of early diagnosis.

In conclusion GISTs are commonly diagnosed incidentally during laparotomy due to various aetiological findings. Most GISTs are presented with gastrointestinal bleeding and abdominal pain. Surgical resection with safety margin is still the mainstay of management of GIST. Surgical treatment of incidentally discovered advanced GISTs presenting with unresectable primary lesion or metastasis carried very poor prognosis even with the use of postoperative neoadjuvant therapy.

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Table (1):Tumor's localization

Localization	Patients(n)	(%)
Gastric	7	64
Jejunal	2	18
Ileal	1	9
Duodenal	1	9

Table (2): Symptoms and clinical presentation

GIST localization	Clinical presentation			
	GI bleeding	Abdominal pain	GI Obstruction	Palpable mass
Gastric	4	2	-	1
Jejunal	-	1	1	-
Ileal	-	1		-
Duodenal	-		1	-

Table (3): Operative findings and histopathologic study

GIST localization	Operative finding			Extent of resection			Mitotic activity (/50HPF)		
	Resectable without metastasis	Resectable with metastasis	Irresectable with metastasis	RO	R1	Irresectable	<5	5-10	>10
Gastric	6	1 (liver metastasis)	-	5	2	-	4	2	1
Jejunal	1	1 (liver metastasis)	-	2	-	-	1	1	-
Ileal	1	-	-	1	-	-	1	-	-
Duodenal	-	-	1 (peritoneal metastasis)	-	-	1	-	-	1
Total	8	2	1	8	2	1	6	3	2

Table (4): Postoperative morbidity and mortality

	Gastric GIST	Jejunal GIST	Ileal GIST	Duodenal GIST	Total No.
Wound infection	1			1	2
Wound dehiscence		1			1
Prolonged ileus			1		1
Local recurrence	2				2
Mortality	1			1	2

Fig.1: upper endoscopy showing gastric GIST with intact mucosa

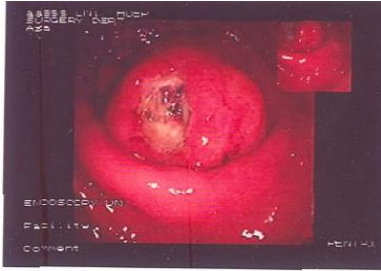


Fig.2: upper endoscopy showing ulcerating gastric GIST.



Fig3: CT abdomen showing small intestinal GIST



Fig.4: gastric GIST



Fig.5: Resected gastric GIST (11cm in diameter)