

Malignant Gastrointestinal Stromal Tumors of the Stomach

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ABSTRACT:

BACKGROUND:

Stromal or mesenchymal neoplasms affecting the gastrointestinal (GI) tract are divided into two groups. The less common variety includes tumors that are identical to those that arise in the soft tissues throughout the rest of the body, including lipomas, schwannomas, hemangiomas. The second more common group consists of stromal tumors that are collectively referred to as gastrointestinal stromal tumors (GISTs).

They are most often located in the stomach and proximal small intestine.

OBJECTIVE:

To compare the incidence, mode of presentation and management of malignant gastric GISTs of this study from Iraq with other world reports.

METHODS:

Retrospective study of the medical records of 1037 patients with gastric malignancies operated upon between January 1970-December 2000 were reviewed. The incidence of GISTs, their age and sex, symptomatology, diagnostic procedures, surgical management and results will be presented.

RESULTS:

Among 1037 patients with gastric malignancies, 13 (1.25%) were malignant GISTs. 6 were males and 7 females. Age ranges from 19-67 (median 58 +/- 13.2397 SD) years. Mode of presentation were; upper GI bleeding 8(62%), dyspepsia 4(31%) and mass one (8%) patient. Duration of illness ranges from 2 days-8 years (median 3 months

+/- 25.9207 SD). Barium study revealed a tumor in 10 out of 11 patients. Endoscopy in 12 patients reported 4 nodular, 3 fungating and 3 ulcerative tumor and two normal. Ultrasound in 8 patients showed a mass in 7(5 intraluminal, two extraluminal) and no tumor in one. Site of tumor were the; lesser curve 4(31%), antrum 3(23%), greater curve 2(15%), fundus 2(15%), body one (8%) and cardia one (8%) patient. Grossly the tumors were; fungating 5, nodular 2, ulcerative one, nodular-cystic 3 and nodular-ulcerative in 2. The tumor size vary from 5x3 – 17x12 (mean 9.69231 +/- 3.727793 SD x 7.69231 +/- 2.95479 SD) cm.

Gastric resections were; upper 5, segmental 4, subtotal 2 and lower 2 patients. Chemotherapy and/or radiotherapy were given to advance or those with metastasis. Histopathology reported low-grade malignancy in 5 and high-grade in 8 patients. According unified 1997 TNM staging were; I 2, II 4, III 3 and IV 4 cases. Two-years survival was 69% (9 out of 13) and 5-years was 46% (6 out of 13).

CONCLUSION:

Malignant GISTs constitute 1.25 % of all gastric malignancies. No gender predilection found. Median age 50.3 years. Recurrent upper GI bleeding in 62% and dyspepsia in 31%. No specific symptoms but abdominal mass in 4 cases. Barium study, endoscopy and US were the diagnostic procedures. Tumors were; mostly intraluminal, fungating nodular and large (median 8x8 cm). Resection was the treatment. 5 were low-grade and 8 high-grade malignancy. 2 and 5-years survival were 62% and 46% respectively.

KEY WORDS: Malignant Gastric GISTs, Gastrointestinal, Gastrointestinal Tract

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INTRODUCTION:

Gastrointestinal stromal tumors (Gists) are rare and account for 0.1-3 % of all gastrointestinal neoplasms (GIN).^[1, 2] GISTs were classified as smooth-muscle tumors, namely leiomyomas, leiomyoblastoma, leiomyosarcoma and schwannoma as a result of their histological findings and apparent origin in muscularis propria of the gastrointestinal tract

(GIT), until 1983 when electronmicroscopy and immunohistochemistry findings demonstrated a lack of smooth-muscle and schwannoma cells.^[3,4] GISTs are now defined as spindle cell, epitheloid or occasionally pleomorphic mesenchymal tumors of the GIT, characterized by cell-surface expression of the tyrosine kinase KIT protein (CD117, stem cell factor receptor) detected by immunohistochemistry.^[1,5] These tumors start in special cells in the wall of the GIT called "interstitial cell of Cajal's" (ICCs) or in very primitive cells (stem) that can develop into ICCs, these cells are part of the autonomic nervous system which send signals to the GIT and so sometimes called the "pacemakers" of the GIT.^[6,7] The term leiomyoma "smooth-muscle tumours" remain accurate only in the esophagus and are the most common mesenchymal tumor in the esophagus while it is rarely seen in the stomach and small bowel, in contrast GISTs are rare in the esophagus and are common in the stomach and small bowel.^[8] GISTs occur throughout the GIT but most common in the stomach (60-70%) and the small bowel (25-35%) with rare occurrence in the colon & rectum (5%), esophagus (<2%) and appendix.^[9] GISTs account for approximately 80% of mesenchymal tumors.^[6] Regarding the detection and localization of upper GI of mesenchymal, endoscopic ultrasonography considered the best diagnostic modality in compared with endoscopy, barium contrast study, ultrasonography, CT, and, MRI.^[10] Endosonographically, GISTs is typically a well circumscribed hypoechoic, homogenous mass that can arise from either the second hypoechoic layer (muscularis mucosa) or the fourth hypoechoic layer (muscularis propria). GISTs, leiomyomas, and schwannomas can not be differentiated with EUS without special immunohistochemical tissue staining. The sensitivity and accuracy of diagnosing GISTs has been reported as 95% and 87%, respectively.^[11] When malignant changes occur, GISTs show heterogeneous echo texture with hyperechoic deposits and/or anechoic necrotic zones inside large tumors. According to the one report, EUS findings of tumor size greater than 4 cm, an irregular extraluminal border, echogenic, and anechoic spaces are good indicators of malignancy. The sensitivity ranged between 80% and 100% in detecting malignancy, when at least two out of four features were presents. In addition to the EUS, EUS guided fine needle aspiration (EUS-FNA) can be performed

for immunohistochemical examination to achieve better diagnostic accuracy.^[12]

Most GISTs (70-80%) are benign, however a continuation from benign to malignant can be predicted, according to the tumor size and the number of mitosis per high power microscope field.^[9] The three most common of primary malignant gastric neoplasms are adenocarcinoma (95%), lymphoma (4%) and malignant GISTs (1%), other rare primary malignancies include carcinoid, angiosarcoma, carcinosarcoma and squamous cell carcinoma.^[13]

PATIENTS AND METHODS:

The medical records of 1037 patients with histologically proved malignant gastric neoplasms operated upon by the senior author between January 1970-December 2000 at the Medical City Hospital and Al-Mustansiria Hospital, Baghdad were reviewed.

The incidence of gastric GISTs, their age and sex, mode of presentation, symptoms and signs, diagnostic methods used, surgical procedures, grade of malignancy, staging and results, will be compared with other reports.

RESULTS:

Among 1037 patients with malignant gastric neoplasms 13(1.25%) were GISTs, others not included in this article were; 878(84.7%) adenocarcinoma, 139(13.4) lymphoma, 4(0.39%) leiomyoblastoma, 2(0.2%) carcinoid and one(0.1%) melanoma.

There were; 6 males and 7 females. Age ranges from 19-67 years, average (median) 50.30769 (58 +/- 13.23971[SD]) years. Mode of presentation were; upper GI bleeding 8(61.5%), dyspepsia 4(30.8%) and abdominal mass 1(7.7%). The upper GI bleeding were; recurrent hematemesis and melena in 4, recurrent melena in 2 and first episode of melena in another 2 patients. Other symptoms and sign were; anorexia 6(46%), vomiting 5(38.5%), pain 4(30.8%), abdominal mass 4(30.8%), weight loss 3(23%) and satiety 3(23%) patients. Duration of symptoms vary from 2 days-8years, average (median) 10.32331 (3 +/- 25.92072 [SD]) months. Hb ranges from 6.8-16 Gm/100ml, average (median) 10.01538 (9 +/- 3.01132[SD]) Gm/100ml. Barium study revealed the tumor in 10 out of 11 patients. Endoscopy in 12 patients reported tumor in 10 (4 nodular, 3 fungating, 3 ulcerative) and no tumor seen in 2. Ultrasound on 8 patients showed intraluminal mass in 5, extraluminal in 2 and one normal. Site of tumor were

in; lesser curve 4, antrum 3, greater curve 2, fundus 2, cardia one and body in one patient.(figure 1 and 2) Gross appearance of the tumors were; fungating 4, nodular-cystic 3, nodular-ulcerative 2, nodular 2, polypoid one and ulcerative in one. The size of tumors ranges from 5x3-17x12 cm, average (median) 9.69231 x 7.69231 (8x8) cm.

Types of gastrectomy were; upper in 5, segmental in 4, subtotal in 2 and lower in 2 cases. Only one patient with peritoneal metastasis had lymph nodes involvements.

Histopathology reported malignant GISTs, 5 were low-grade and 8 were high-grade.

Staging according to modified 1997 TNM were; I two, II four, III three and IV four cases.(Table 1) Patients with tumors stage III and IV were given chemotherapy and/or radiotherapy without noticeable outcome. The two and 5-years survival versus the stage of tumor, grade of malignancy and size of the tumor is shown in table 2. The overall two and 5-years survival were 69% and 46% respectively.

DISCUSSION:

Mesenchymal neoplasms of the GIT are uncommon and represent a small percentage of all GIT neoplasms. Mesenchymal neoplasms include a variety of tumors located within the muscularis mucosa or submucosa, of these the most common are the GISTs, however a variety of others including smooth muscle (leiomyomas), neural (schwannomas, neurofibroma) and vascular (haemangiomas) tumors. Most of these tumors are benign, although their counterparts have been reported^(3,4, 8,)

The concept of GISTs had changed since 1983 when it was discovered that the cells of these tumors express the Kit protein (CD 117, stem cell factor).^[3]

The GISTs shows striking morphological and immunophenotypic similarities with ICC and that may originate from stem cells that differentiate toward a pace maker cell phenotype, it was proposed by Kindblom et al (1998) to replace its name by gastrointestinal pacemaker cell tumor (GITPACT).

Gastric leiomyoblastoma were excluded from GISTs, as it does not differentiate to Cajal's cells but to smooth muscle cells.^[14,15,16] Thus why four patients with leiomyoblastoma were excluded from this study.

The incidence of malignant gastric GISTs among all gastric malignancies in this series

is 1,25% which is in line with other reports 1-3%.^[3,13]

Sex incidence revealed male prevalence in most reports while our study showed no sex predilection^[1,2,17,18,19] The age incidence in this study

ranges from 19-67 (only two patients were under 40) years with a mean age of 50.3 years which close to most other studies^[1,3,17,20,21]

The leading presentation in our study was upper gastrointestinal bleeding in 8(61.5%) patients which is higher than other studies. Bleeding occur usually in large tumors secondary to necrosis in its centre and ulceration.^[1] Most symptoms are not specific such abdominal pain, anorexia, vomiting, weight loss and satiety that were reported in this study is similar to other articles.^[1,17,19]

Small GISTs are usually asymptomatic in most patients and sometimes seen accidentally during operations, but when it increase in size, it produce symptom either as a result of ulceration and bleeding or its size cause obstruction or pressure symptoms. Duration of symptoms vary from few days in those with acute bleeding and obstruction or years in others with mild symptoms. Preoperative histological diagnosis was difficult in the past by endoscopy and biopsy or by FNA biopsy which carries risk of implantation, but recently the use of EUS alone or EUS-FNA biopsy sample with a 19- or 22- needle was effective diagnostic method.^[1,10,11,12,18]

Diagnosis in this study was carried out by two senior experienced pathologists before the era of EUS and the malignancy of these tumors were assessed by the number of mitosis per high power microscope.

Most GISTs were located in proximal part of stomach.^[19] Such a finding were noticed in our study, 9 tumors were located in the upper half of the stomach and only 3 (23%) in antrum, thus why 7 cases were treated by upper or subtotal gastrectomy. (table 1)

The correct surgical treatment for most malignant GISTs is local resection without lymphadenectomy as involvement of lymph nodes is controversial, some deny its existence others say it is rare (2-6%).^[1,2,9,19]

Local resection with a surrounding cuff of 1-2 cm is safer than enucleation as this might cause spillage and lead to recurrence. Formal gastrectomy with lymphadenectomy is preferable for large tumors.^[1,19] Complete surgical resection remains the mainstay of treatment and should be the goal initially, as chemotherapy and radiation are ineffective.^[19,20,21]

In 2001 a promising new drug Imatinib (STI571), a tyrosine kinase inhibitor licensed for treatment of unresectable or metastatic malignant GISTs and is currently undergoing clinical trials with encouraging reports.^[1,22] Unfortunately our patients were treated before the era of Imatinab.

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CONCLUSION:

Malignant GISTs are rare. The stomach is the commonest site in the GIT. Most patients present over 40 years of age (median 50.3yrs). Sex equally affected. Small tumors are asymptomatic and mostly benign but a continuum to malignant can be predicted with increase in size, thus why incidental findings of such tumors should be excised widely. Symptoms appear with the increase in tumor size, either it ulcerate and bleed or cause pressure and/or

obstruction. Malignant gastric GISTs metastasize chiefly to the liver and peritoneum but rarely to regional lymph nodes. Diagnosis can be achieved by; US, C-T, endoscopy and EUS-biopsy. Complete surgical resection remains the only path to offer a high percent cure as chemotherapy and radiation are ineffective. Recently tyrosine kinase inhibitor (Imatinib) proved effective for locally advanced tumors and metastasis.

Table 1: Compare the relation of the tumor-stage, type of resection, size of tumor and grade of malignancy with the outcome.

Case	T	N	M	Stage*	Gastrectomy	T-size cm	Histo. grade	Follow-up
1	T1	N0	M0	IA	lower	5 x 3	low	No recurrence > 5 yrs
2	T2	N0	M0	IB	segmental	5 x 5	low	No recurrence > 5 yrs
3	T4	N0	M1 Perito	IV	upper	11 x 6	high	Died after 8 mo
4	T4	N0	M0	IIIA	lower	8 x 8	high	Local recurrence died after 28 mo
5	T3	N0	M0	II	segmental	9 x 8	low	No recurrence > 5 yrs
6	T3	N0	M0	II	subtotal	9 x 9	high	No recurrence > 5 years
7	T4	N0	M1 liver	IV	subtotal	7 x 5	high	Died after 15 mo from liver sec.
8	T4	N0	M0	IIIA	segmental	17 x 12	high	Died from perito sec after 18 mo
9	T3	N0	M0	II	upper	13 x 10	high	Local recurrence died after 22 mo
10	T3	N0	mo	II	upper	13 x 11	high	No recurrence > 5 yrs
11	T4	N0	M1 liver	IV	upper	15 x 12	low	Died after 38 mo from liver sec
12	T4	N0	M0	IIIA	upper	7 x 5	low	No recurrence > 5 yrs
13	T4	N2	M1 perito	IV	segmental	5 x 5	High	Died after 9 mo from perito sec

*modified 1997 TNM staging

Table 2: Two & five-years survival versus Stage of tumor, Grade of Malignancy and Size of tumor.

Survival	Stage (TNM)					Grade (malignancy)		Size of tumor (cm)		
	I n3	II n4	III n4	IV n2	n4	Low n5	High n8	< 6 n3	6-9 n5	10... n5
% 2-years	100	100	66	25		100	50	67	80	40
% 5-years	100	75	33	0		80	25	67	60	20

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