World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v17.i14.1836

World J Gastroenterol 2011 April 14; 17(14): 1836-1839
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

BRIEF ARTICLE

Gastrointestinal stromal tumors: Thirty years experience of an Institution

Simone Arolfo, Paolo Mello Teggia, Mario Nano

Simone Arolfo, Paolo Mello Teggia, Mario Nano, Department of Clinical and Biological Sciences, San Luigi Gonzaga Teaching Hospital, University of Turin-Second School of Medicine, Reg. Gonzole 10, 10043 Orbassano, Turin, Italy
Author contributions: Arolfo S designed the study and collected data; Arolfo S, Mello Teggia P and Nano M analyzed data; Arolfo S and Nano M wrote the article.
Correspondence to: Simone Arolfo, MD, Department of Clinical and Biological Sciences, San Luigi Gonzaga Teaching Hospital, Reg. Gonzole 10, 10043 Orbassano, Turin, Italy. simone.arolfo@tiscali.it
Telephone: +39-11-9026307 Fax: +39-11-9026887
Received: August 19, 2010 Revised: September 27, 2010
Accepted: October 4, 2010
Published online: April 14, 2011

Abstract

AIM: To report our experience of gastrointestinal stromal tumors (GISTs) during the last 29 years.

METHODS: Thirty two cases of GIST referred to our Institution from the 1st January 1981 to the 10th June 2010 were reviewed. Metastases, recurrence and survival data were collected in relation to age, history, clinical presentation, location, size, resection margins and cellular features.

RESULTS: Mean age was 63.7 years (range, 40-90) and incidence was slightly higher in males (56%). R0 resection was performed in 90.7% of cases, R1 in 6.2% (2 cases) and R2 in 3.1% (one case). Using Fletcher's classification 8/32 (25%) had high risk, 9/32 (28%) intermediate and 15/32 (47%) low risk tumors. Follow-up varied from 1 mo to 29 years, with a median of 8 years; overall survival was 75% (24/32), disease-free survival was 72% and tumor-related mortality was 9.3%. Three patients with high risk GIST were treated with imatinib mesylate: one developed a recurrence after 36 mo, and 2 are free from disease at 41 mo.

CONCLUSION: Surgical treatment remains the gold standard therapy for resectable GISTs. Pathological and biological features of the neoplasm represent the most important factors predicting the prognosis.

Keywords: Gastrointestinal stromal tumors; Fletcher's classification; Resection margins; Recurrence

Peer reviewer: Dr. Gerardo Rosati, Department of Medical Oncology, S. Carlo Hospital, Via Potito Petrone, 1, Potenza 85100, Italy

Arolfo S, Mello Teggia P, Nano M. Gastrointestinal stromal tumors: Thirty years experience of an Institution. *World J Gastroenterol* 2011; 17(14): 1836-1839 Available from: URL: http://www.wjgnet.com/1007-9327/full/v17/i14/1836.htm DOI: http://dx.doi.org/10.3748/wjg.v17.i14.1836

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are mesenchymal tumors that arise from the gastrointestinal tract and account for < 1% of all gastrointestinal neoplasms[1,2]. The term "stromal tumor" was first used by Mazur and Clark[3] in 1983; later the acronym GIST was introduced[4,5] to define a well established pathological entity, whose constitutive elements derive from the interstitial cell of Cajal, an intestinal pacemaker cell, and express a highly specific marker called KIT (CD117).

The estimated incidence of GISTs is approximately 10-20 per million people annually worldwide[6]. This tumor affects men slightly more often than women and the mean age at the time of diagnosis is 60 years[7,8]. The majority of GISTs arise in the stomach (60%) and small bowel (30%); the remaining 10% in the esophagus and rectum[9].

Clinical presentation is heterogeneous, even if GISTs are usually asymptomatic and are diagnosed incidentally during endoscopy, radiological imaging or abdominal exploration[10,11]. Preoperative biopsy is not recommended for resectable masses[12], because of the fragility and predisposi-

tion to hemorrhage of these masses, and the possibility that the biopsy needle touches a necrotic portion of the tumor. Biopsy is justified only for masses preoperatively judged unresectable, in that a definitive pathological diagnosis would allow medical treatment using imatinib to commence.

Surgery represents the gold standard treatment for resectable GISTs. Principles of a correct procedure include negative margins on the specimen and integrity of the pseudocapsule[13]. GISTs do not metastasize through lymphatic spread, so systematic lymphadenectomy is not indicated.

Survival after 5 years is extremely variable in the reported series, ranging from 48% to 80%. 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. Imatinib mesylate was first used as medical therapy for GIST in 2000[14]. Several clinical trials later confirmed that imatinib was safe and effective in the treatment of advanced and metastatic GISTs[15-17]. In 2009 the American College of Surgeons Oncology Group presented the results of a randomised Phase III Multicentre Trial that showed the effectiveness of imatinib as adjuvant therapy for primary GISTs in term of recurrence free and overall survival[18].

The purpose of this study is to analyze pathological features and treatment modality of 32 cases of GIST operated on at San Luigi Teaching Hospital (Turin) during the last 29 years.

MATERIALS AND METHODS

The study is a retrospective analysis of 32 cases of GIST referred to our Institution between 1st January 1981 and 10th June 2010. In every case, the diagnosis of GIST was confirmed by a positive immunohistochemical assay for CD117. Before GISTs were recognized as well defined pathological entities and the CD 117 assay was available, GISTs were diagnosed as leiomyoma, fibroleiomyoma or leiomyosarcoma. All specimens labeled with these diagnoses were tested for CD 117 and the positive ones classified as GISTs and included in the study. In this group, metastases, recurrence and survival data were collected in relation to age, history, clinical presentation, location, size, resection margins and cellular features such as mitotic index and immunohistochemistry (Table 1).

RESULTS

During the last 29 years, 32 patients underwent surgical intervention for GIST at San Luigi Teaching Hospital. Mean age was 63.7 years (range, 40-90) and prevalence was slightly higher in males (56%). Among males the mean age was 62, while among females it was 66. Gastrointestinal bleeding with acute or chronic anemia represented the most common clinical presentation (16 cases, 50%), followed by non-specific abdominal pain (12 cases, 37.5%), dysphagia (one case, 3.1%) and lumbar pain (one case, 3.1%); in 2 cases (6.3%) GISTs were found incidentally on the resected specimen. The medical histories did not show any association between GISTs and associated pathologies, which were extremely heterogeneous.

The majority of tumors were located in the stomach (18 cases, 56.3%); 2 in the antrum, 3 in the fundus, 13 in the corpus (5 in the anterior wall, 3 in the posterior wall, 2 along the great curve and 3 along the small curve). The others were found in the small bowel (10 cases, 31.3%; 7 in the ileum, 2 in the jejunum and one in the duodenum), mesentery (2 cases, 6.2%), esophagus (one case, 3.1%) and rectum (one case, 3.1%). Tumor size varied between 1 and 30 cm, with a mean diameter of 7 cm. Even though wedge or segmental resection was the most frequent surgical procedure, one anterior rectal resection, 4 total gastrectomies, one subtotal and one extended to the pancreatic tail, were performed. Only 4 operations (12.5%) were executed laparoscopically for tumors with a mean diameter of 4.5 cm: one segmental resection of the ileum and 3 gastric resections, one of which was converted. R0 resection was performed in 90.7% of the cases, R1 in 6.2% (2 cases) and R2 in 3.1% (one case). Using Fletcher's classification[19], 8 out of 32 cases (25%) were high risk, 9 (28%) intermediate and 15 (47%) low risk tumors.

Follow-up varies from 1 mo to 29 years, with a median of 8 years. To date, 24 patients (75%) are alive; 8 patients (25%) died: 3 patients (9.3%) died due to recurrence at 13, 14, and 36 mo after the first operation, one died from lung cancer, 2 from gastric cancer, one from gallbladder cancer and one died of AIDS. Among the 24 surviving patients, only one, who had a high risk GIST, developed a recurrence and underwent a second surgical intervention, so that to date 23 patients (72%) are actually free from disease. If we consider a 3-year follow-up, we can include 25 patients from our series. In this group overall survival is 68% (17 out of 25) and disease-free survival is 64% (16 out of 25).

The rate of metastatic disease did not exceed 9.3% (3 cases); in 2 cases the primary tumor was a high risk GIST (a rectal GIST with liver metastasis and a mesenteric GIST with ileal metastasis), but, interestingly, in one case the patient was affected by a low risk jejunal tumor with lung metastasis.

Two patients underwent an R1 resection and one an R2 resection; they were treated with imatinib mesylate: one patient (R2) developed a recurrence after 36 mo that required a second surgical intervention followed by continued therapy with imatinib (no other tyrosine kinase inhibitors were available); 2 patients (R1) are free from disease at 41 mo. Tumors were located in the rectum, ileum and stomach, respectively.

DISCUSSION

During the last 10 years, since the GIST has been recognized as a well-defined pathological entity with its own characteristics, the surgical management of GISTs has changed. The lack of lymphatic spread of this kind of tumor makes lymphadenectomy unnecessary, so the only oncological criteria is to maintain the integrity of the capsule and to perform an R0 resection. Wedge resection is a correct procedure from an oncological point of view, but if technically unfeasible, as for esophageal or rectal GISTs, a segmental resection becomes necessary. Our experience was over a period of 29 years. Patients operated before 2000 underwent more extensive resections than patients operated after 2000, without any difference in overall survival or disease-

Table 1 Distribution of gastrointestinal stromal tumors by site and their features

Organs	Number of cases	Low risk	Moderate risk	High risk	Mitotic index > 5 × 50 HPF	Mean size (cm)	CD117+	CD34+	Ki67 > 10%
Esophagus	1	1	/	/	/	2.5	1	/	/
Stomach	18	11	6	1	5	5.4	18	8	7
Duodenum	1	/	1	/	/	5.0	1	/	/
Jejunum	2	1	/	1	1	8.4	2	1	1
Ileum	7	2	2	3	3	9.7	7	4	4
Rectum	1	/	/	1	1	15.0	1	1	1
Mesentery	2	/	/	2	1	8.0	2	1	1
Total	32	15	9	8	11	7.0	32	15	14

HPF: High power field.

free survival. The types of intervention were extremely heterogeneous, demonstrating that there is no standardized procedure to approach this kind of neoplasm. Epidemiological features found in our series are comparable with the literature: DeMatteo *et al*[20] reported a median age of 58, with predominant localization of the tumors in the stomach (39%) followed by small bowel (32%); Ahmed *et al*[21] reported a mean age of 64.4, with tumors mainly localized in the stomach (52%) and colon (13%). Clinical presentation is extremely heterogeneous in the literature as in our series: a recent Swedish study demonstrated that 70% of GISTs had associated symptoms, 20% had none and 10% were detected at autopsy[22]. Symptoms were generally non specific: nausea, vomiting, abdominal pain or discomfort; sometimes GISTs caused gastrointestinal bleeding, because of the erosion of gastric or small bowel mucosa; dysphagia occurred rarely, and was associated with a tumor located in the esophagus; biliary obstruction could occur if the tumor was located in the duodenum; and intussusception, could occur if the tumor was located in the small bowel.

The R0 resection rate was higher in our series (90.7%) than in others: DeMatteo *et al*[20] reported 47%; Ahmed *et al*[21] 51%. The difference can be explained by the larger number of patients in those series and the larger number of locally advanced or metastatic GISTs treated. In our series, 9.3% of the patients died of disease. Ahmed reported 11% with a mean follow-up of 6.8 years and De Matteo 50% with a mean follow-up of 24 mo. The difference is due to the large number of patients with GISTs at low and moderate risk of relapse in our series compared with that of De Matteo.

Four laparoscopic operations (12.5%) were performed in our series for tumors with a mean diameter of 4.5 cm located in the anterior wall of the stomach and in the jejunum; none of these patients developed local or distant recurrence. DeMatteo and Ahmed did not deal with a laparoscopic approach to GISTs. Even if our laparoscopic series is limited to 4 operations we report results of other series, avoiding every comparison with our own. Novitsky *et al*[23] reported a series of 50 laparoscopic gastric resections for GISTs. Mean diameter of the neoplasm was 4.4 cm; the conversion rate was 0% and disease-free survival 92% at 36 mo. Huguet *et al*[24] reported a series of 33 patients affected by gastric GISTs of mean diameter of 3.9 cm and treated with a laparoscopic approach. The conversion rate was 6% and disease-free survival 100% with a median follow-up of 13 mo. Similar results were obtained by Basu *et al*[25], Nishimura *et al*[26] and Pitsinis *et al*[27]. Tabrizian *et al*[28] reported a series of 76 laparoscopic resections for GISTs. Of these, 72% were located in the stomach and 28% in the small bowel, with mean diameter of 4.2 and 3.9 cm, respectively. The conversion rate was 14% and disease-free survival 78% at 41 mo (77% gastric *vs* 82% small bowel). Laparoscopic treatment of GIST is a safe and effective procedure, but should only be performed at centers with excellent laparoscopic experience, taking strict oncological precautions to avoid rupture of the pseudocapsule and spreading of neoplastic cells. If these precautions cannot be assured, the surgeon must not hesitate to convert, because this kind of mistake can change a curable disease into a poor prognostic one and this must be avoided. International guidelines recommend the employment of laparoscopic surgery only for tumors smaller than 5 cm[13].

In conclusion, surgical treatment remains the gold standard therapy for resectable GISTs. Surgical strategies are different and heterogeneous, as the only oncologic criteria imposes the preservation of the integrity of the capsule and the avoidance of infiltration of the resection margins. The laparoscopic approach is considered safe and effective for masses not exceeding 5 cm, in centers experienced in advanced laparoscopic surgery. In the presence of resectable and non metastatic masses, correctly removed by the surgeon, pathological and biological features of the tumor, expressed by Fletcher's classification, remain the most important factors for predicting the prognosis. For high risk or metastatic tumors as for non resectable masses, molecular therapy with the tyrosine kinase inhibitor imatinib mesylate has improved survival. The use of the laparoscopic technique in combination with molecular therapy will permit the development of a minimally invasive treatment for this type of neoplasm, improving patients' survival and quality of life.

COMMENTS

Background

Gastrointestinal stromal tumors (GISTs) are tumors arising from the wall of the gastrointestinal tract, from the esophagus to the rectum. As in the heart, where pacemaker cells regulate the beat, so in the intestinal tract there are similar pacemaker cells regulating intestinal motility (peristalsis) called interstitial cells of Cajal. GISTs are a neoplastic proliferation of this kind of cell and account for < 1% of all gastroin-

testinal tumors.

Research frontiers

A correct definition of GIST is quiet recent. During the last 15 years knowledge about the biological behavior and natural history of these tumors has improved, but treatment is not yet perfectly standardized.

Innovations and breakthroughs

The purpose of this article is to report the cases of GIST treated during the last 29 years at San Luigi University Hospital. Many changes occurred in diagnosis and treatment, but it is possible to extract from these data relevant information about epidemiology, natural history and therapy of GISTs. Data are comparable with other important series from the USA, UK, and Japan. The authors can conclude that surgical treatment remains the gold standard therapy for resectable tumors. For advanced or metastatic GISTs medical therapy with imatinib mesylate, an inhibitor of tyrosine kinase, is safe and effective.

Applications

The study is a further confirmation of the epidemiological features and correct treatment modality for GISTs.

Terminology

Stromal refers to the connective tissue, that is the structural tissue of the organs. Tyrosine kinases are molecules implicated in cell proliferation and tyrosine kinase inhibitors block this cellular pattern, controlling tumor proliferation.

Peer review

The article presented by the authors is interesting.

REFERENCES

1 **Howe JR**, Karnell LH, Scott-Conner C. Small bowel sarcoma: analysis of survival from the National Cancer Data Base. *Ann Surg Oncol* 2001; **8**: 496-508

2 **van der Zwan SM**, DeMatteo RP. Gastrointestinal stromal tumor: 5 years later. *Cancer* 2005; **104**: 1781-1788

3 **Mazur MT**, Clark HB. Gastric stromal tumors. Reappraisal of histogenesis. *Am J Surg Pathol* 1983; **7**: 507-519

4 **Ueyama T**, Guo KJ, Hashimoto H, Daimaru Y, Enjoji M. A clinicopathologic and immunohistochemical study of gastrointestinal stromal tumors. *Cancer* 1992; **69**: 947-955

5 **Miettinen M**, Virolainen M, Maarit-Sarlomo-Rikala. Gastrointestinal stromal tumors--value of CD34 antigen in their identification and separation from true leiomyomas and schwannomas. *Am J Surg Pathol* 1995; **19**: 207-216

6 **Kindblom LG**, Remotti HE, Aldenborg F, Meis-Kindblom JM. Gastrointestinal pacemaker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. *Am J Pathol* 1998; **152**: 1259-1269

7 **Kindblom LG**. Gastrointestinal stromal tumours; diagnosis, epidemiology, prognosis. In: ASCO Annual Meeting, Chicago, 2003

8 **Dal Corso H.M.,** Solej M, Nano M. Giant gastrointestinal stromal tumour of the stomach in an elderly patient. *J Gastroint Surg* 2007;**11**: 804-806

9 **Katz SC,** DeMatteo RP. Gastrointestinal Stromal Tumours and Leiomyosarcomas. *J of Surg Oncol* 2008;**97**: 350–359

10 **Everett M**, Gutman H. Surgical management of gastrointestinal stromal tumors: analysis of outcome with respect to surgical margins and technique. *J Surg Oncol* 2008; **98**: 588-593

11 **Gupta P**, Tewari M, Shukla HS. Gastrointestinal stromal tumour. *Surgical Oncology* 2008; **17**: 129-138

12 **Nowain A**, Bhakta H, Pais S, Kanel G, Verma S. Gastrointestinal stromal tumors: clinical profile, pathogenesis, treatment strategies and prognosis. *J Gastroenterol Hepatol* 2005; **20**: 818-824

13 **Demetri GD,** Benjamin RS, Blanke CD, Blay JY, Casali P, Choi H, Corless CL, Debiec-Rychter M, DeMatteo RP, Ettinger DS, Fisher GA, Fletcher CD, Gronchi A, Hohenberger P, Hughes M, Joensuu H, Judson I, Le Cesne A, Maki RG, Morse M, Pappo AS, Pisters PW, Raut CP, Reichardt P, Tyler DS, Van den Abbeele AD, von Mehren M, Wayne JD, Zalcberg J. NCCN Task Force report: management of patients with gastrointestinal stromal tumor (GIST)-update of the NCCN clinical practice guidelines. *J Natl Compr Canc Netw* 2007; **5**(Suppl 2):s1-s29

14 **Joensuu H**, Roberts PJ, Sarlomo-Rikala M, Andersson LC, Tervahartiala P, Tuveson D, Silberman S, Capdeville R, Dimitrijevic S, Druker B, Demetri GD. Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. *N Engl J Med* 2001; **344**: 1052-1056

15 **van Oosterom AT**, Judson I, Verweij J, Stroobants S, Donato di Paola E, Dimitrijevic S, Martens M, Webb A, Sciot R, Van Glabbeke M, Silberman S, Nielsen OS. Safety and efficacy of imatinib (STI571) in metastatic gastrointestinal stromal tumours: a phase I study. *Lancet* 2001; **358**: 1421-1423

16 **Demetri GD**, von Mehren M, Blanke CD, Van den Abbeele AD, Eisenberg B, Roberts PJ, Heinrich MC, Tuveson DA, Singer S, Janicek M, Fletcher JA, Silverman SG, Silberman SL, Capdeville R, Kiese B, Peng B, Dimitrijevic S, Druker BJ, Corless C, Fletcher CD, Joensuu H. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med* 2002; **347**: 472-480

17 **Verweij J**, Casali PG, Zalcberg J, LeCesne A, Reichardt P, Blay JY, Issels R, van Oosterom A, Hogendoorn PC, Van Glabbeke M, Bertulli R, Judson I. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. *Lancet* 2004; **364**: 1127-1134

18 **DeMatteo RP,** Ballman KV, Antonescu CR, Maki RG, Pisters PWT, Demetri GD, Blackstein ME, Blanke CD, von Mehren M, Brennan MF, Patel S, McCarter MD, Polikoff JA, Tan BR, Owzar K, on behalf of the American College of Surgeons Oncology Group (ACOSOG) Intergroup Adjuvant GIST Study Team. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. *Lancet* 2009;**373**:1097–1104

19 **Fletcher CD**, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, Miettinen M, O'Leary TJ, Remotti H, Rubin BP, Shmookler B, Sobin LH, Weiss SW. Diagnosis of gastrointestinal stromal tumors: A consensus approach. *Hum Pathol* 2002; **33**: 459-465

20 **DeMatteo RP**, Lewis JJ, Leung D, Mudan SS, Woodruff JM, Brennan MF. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. *Ann Surg* 2000; **231**: 51-58

21 **Ahmed I**, Welch NT, Parsons SL. Gastrointestinal stromal tumours (GIST)-17 years experience from Mid Trent Region (United Kingdom). *Eur J Surg Oncol* 2008; **34**: 445-449

22 **Nilsson B**, Bümming P, Meis-Kindblom JM, Odén A, Dortok A, Gustavsson B, Sablinska K, Kindblom LG. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era--a population-based study in western Sweden. *Cancer* 2005; **103**: 821-829

23 **Novitsky YW**, Kercher KW, Sing RF, Heniford BT. Long-term outcomes of laparoscopic resection of gastric gastrointestinal stromal tumors. *Ann Surg* 2006; **243**: 738-745; discussion 745-747

24 **Huguet KL**, Rush RM Jr, Tessier DJ, Schlinkert RT, Hinder RA, Grinberg GG, Kendrick ML, Harold KL. Laparoscopic gastric gastrointestinal stromal tumor resection: the mayo clinic experience. *Arch Surg* 2008; **143**: 587-590; discussion 591

25 **Basu S**, Balaji S, Bennett DH, Davies N. Gastrointestinal stromal tumors (GIST) and laparoscopic resection. *Surg Endosc* 2007; **21**: 1685-1689

26 **Nishimura J**, Nakajima K, Omori T, Takahashi T, Nishitani A, Ito T, Nishida T. Surgical strategy for gastric gastrointestinal stromal tumors: laparoscopic *vs* open resection. *Surg Endosc* 2007; **21**: 875-878

27 **Pitsinis V**, Khan AZ, Cranshaw I, Allum WH. Single center experience of laparoscopic *vs* open resection for gastrointestinal stromal tumors of the stomach. *Hepatogastroenterology* 2007; **54**: 606-608

28 **Tabrizian P**, Nguyen SQ, Divino CM. Laparoscopic management and longterm outcomes of gastrointestinal stromal tumors. *J Am Coll Surg* 2009; **208**: 80-86

S- Editor Sun H **L- Editor** Cant MR **E- Editor** Ma WH