

Treatment of gastrointestinal stromal tumors - initial experience

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Rezumat

Tratamentul tumorilor stromale gastrointestinale - experiența inițială

Motivație: Tumorile stromale gastrointestinale (TSGI) reprezintă o categorie de neoplazii care oferă pentru prima dată șansa unui tratament specific (inhibitorii de tirozin-kinază) și oferă noi perspective în abordarea altor tipuri de neoplazii.

Metodă: Înregistrarea prospectivă a datelor clinice, proto-coalelor operatorii, datelor de anatomie patologică, terapiei adjuvante și recidivelor la pacienții cu TSGI internate începând cu ianuarie 2004; prezentăm rezultatele inițiale ale pacienților internați până în decembrie 2008

Rezultate: Cei 18 pacienți au avut localizări ale TSGI la nivel gastric (44,44%), duodenal (11,11%), jejunal (16,67%), colon drept (5,55%) și rectal (22,22%). Nici unul dintre pacienții noștri nu au prezentat metastaze evidente clinic, imagistic sau intraoperator. Toți pacienții au beneficiat de rezecții R0, cu excepția unui pacient cu excizie locală și a altuia cu rezecție anterioară R1, ambii pentru TSGI rectal. Terapia cu Imatinib a fost inițiată postoperator la 4 pacienți. Perioada medie de urmărire postoperatorie a fost de 32 de luni (12-58 luni). Am înregistrat 2 recidive, ambele după TSGI rectale. Ceilalți pacienți sunt fără recidivă și supravegheați în continuare.

Concluzii: Prezentăm rezultatele primilor 5 ani ai unui studiu prospectiv asupra TSGI început în 2004. Rezecția completă și potențialul malign conform indexului Fletcher sunt factorii

prognostici cei mai semnificativi. Tratamentul cu Imatinib poate ameliora prognosticul TSGI incomplet rezecate sau cu potențial malign ridicat.

Cuvinte cheie: tumori stromale gastrointestinale, tratament chirurgical, imatinib

Abstract

Background: Gastrointestinal Stromal Tumors (GIST) offered the first opportunity of a specific treatment in neoplasms (tyrosine-kinase inhibitors) and also a new perspective of management of other neoplasms.

Methods: We have prospectively recorded the clinical characteristics, type of surgery, pathologic findings, adjuvant treatment, and recurrence of the patients with confirmed GISTs admitted between January 2004 and December 2008.

Results: There were 18 patients. Location of the tumor was gastric (44.44%), duodenal (11.11%), jejunal (16.67%), right colon (5.55%) and rectal (22.22%). None of our patients had clinical, imagistic or macroscopic metastases. All the patients had R0 resections, except a patient with local excision and another with R1 anterior resection for rectal GISTs. Postoperatively, 4 patients received Imatinib therapy. The mean follow-up period is 32 months (range 8-58 months); 2 recurrences, both after rectal GISTs. The rest of patients are tumor-free and subjects of prospective follow-up.

Conclusion: We present the first 5 years experience of a prospective study of GIST started in 2004. The complete resection and the malignant potential according to Fletcher index are the most significant prognostic factors. Imatinib treatment may improve outcome in incomplete resected or high risk GISTs.

Key words: gastrointestinal stromal tumor, surgical treatment, imatinib

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Introduction

In 1983 Mazur and Clark introduced the term of GIST for a “non-epithelial tumor group consisting of spindle cells and epithelioid cells” (1,2). Before that, most of the non-epithelial tumors developed in the gastrointestinal tract, from the esophagus to the rectum, had controversial designations; many investigators finding under light microscopy those tumors originating in the muscle layer of the gastrointestinal tract had classified them as smooth muscle tumors and referred to them as “leiomyoma” or “leiomyosarcoma”.

Kindblom established in 1998 that the GISTs originate in a pluripotential mesenchymal stem cell programmed to differentiate into gastrointestinal pacemaker cell responsible for initiating and coordinating gastrointestinal motility: the interstitial cell of Cajal from normal myenteric plexus (3). In the same year, Hirota and his colleagues discovered the c-kit proto-oncogene mutations in these tumors (4) and many authors (5-8) used the expression of c-KIT (CD117) in the tumor cells to define GISTs.

As research progressed, beside the 95% GISTs positive for c-KIT (CD117), it became evident that there is a subset of about 5% of GISTs negative for KIT (7-11). Establishing the diagnosis of KIT-negative GIST is difficult and is based on the location and morphology of the tumor, the results of other immunohistochemical stains and the use of mutational analysis of the kinase genes KIT and platelet derived growth factor receptor alpha (PDGFRA). We review here our experience with the first the first 5 years series of diagnosed GISTs.

Methods

We have prospectively recorded the clinical characteristics, type of surgery, pathologic findings, adjuvant treatment, and recurrence of all the patients with confirmed GISTs on histopathology admitted in “St. Spiridon” University Hospital Iasi between January 2004 and December 2008. Although stromal tumors of the gastrointestinal tract have been treated also before, the year 2004 marked the beginning of CD117 immunohistochemical stain availability in our institution and the first certified GIST diagnostic.

The tumor location was assessed by endoscopy (upper digestive endoscopy for gastric or duodenal tumors; colonoscopy for rectal or colonic tumors); endoscopic biopsy was performed in all patients excepting those with jejunal tumors. Curative resection was defined as the resection of all tumor tissue without evidence of residual tumor; local residual tumor or the presence of distant metastases defined the incomplete resection.

All tissues were fixed in 4% neutral buffered formalin and were embedded routinely in paraffin. Haematoxylin-eosin stained sections were reviewed for detailed histomorphologic aspects, and all tumors were classified based on the consensus approach defined by Fletcher et al. (12). The size of the tumor, cell types, cell density, CD117 expression, the number of mitoses in 50 high-power fields (HPF), and of Ki-67 index (over-expression defined as >10% nuclear staining) were recorded (13). We also studied reactions with CD34, SMA, and S-100

proteins for differential diagnosis (14 -16). Recurrence was defined based on pathological confirmation of local recurrence or on definite imagistic evidence.

Results

There were 18 patients diagnosed with GIST in our unit between 2004 and 2008, 11 women (61.11%) and 7 men (38.88%). Median age at the time of diagnosis was 60 years (range 42–77 years). Location of the tumor was gastric (8 patients – 44.44%), duodenal (2 patients – 11.11%), jejunal (3 patients – 16.67%), right colon (1 patient – 5.55%) and rectal (4 cases – 22.22%).

Gastric GIST patients were admitted for abdominal pain, pyrosis, vomiting, gastrointestinal bleeding or anemia. Aspects on barium radiography and ultrasound scan were useful for intragastric location (Fig. 1), but upper digestive endoscopy allowed the definite preoperative diagnostic. For extragastric tumors, the computer tomography (Fig. 2) was the most useful imagistic method. Extragastric GISTs were located on the posterior face (Fig. 3), on the small curve (between the peritoneal layers of the gastrohepatic ligament – Fig. 4) or on the anterior face of the stomach (Fig. 5). Preoperative diagnostic was not definite in those cases. Gastric GISTs were resected by laparoscopy (3 patients – Fig. 6) and open (5 patients – Fig. 7). In all cases, we were able to resect the tumor with a 1-2 cm wide safety margin without performing a standard gastrectomy.

Duodenal GISTs patients were admitted for anemia and epigastric pain. The barium radiography and the upper digestive endoscopy proved the presence of the intraluminal tumor. Endoscopic biopsy was not diagnostic. One of the patients has been treated with pancreatico-duodenectomy with pylor preservation (tumor was located periampullary) and the other one has been treated with local resection (tumor was located on the third portion of the duodenum).

Jejunal GISTs patients were admitted for different sets of complaints. The first patient complaints were pallor, weight loss, loss of appetite. The only abnormal preoperative tests were a moderate anemia and an ultrasound scan of the abdomen that had revealed a 36 mm. diameter hypoechoic structure adjacent to a loop of small intestine, located to the right of the umbilicus and with Doppler signal inside. The tumor was resected by laparoscopy (Fig. 8). The second patient was admitted in emergency and operated for occlusive syndrome. At laparotomy, there was found an intussusception of the jejunum caused by an intraluminal tumor; the affected jejunal segment was resected (Fig. 9). The third patient was known with neurofibromatosis and was admitted in emergency and operated for peritonitis. At laparotomy, there were found 3 jejunal tumors, one of them perforated. The affected jejunal segment (approx. 30 cm. long) was resected.

The single colic GIST patient was admitted for anemia and positive test for occult digestive hemorrhage. The colonoscopy found the tumor on the ascendant colon; it was treated by right hemicolectomy.

There were also 4 patients with rectal GIST, all admitted for rectal tenesmus, constipation, and anorectal pain.

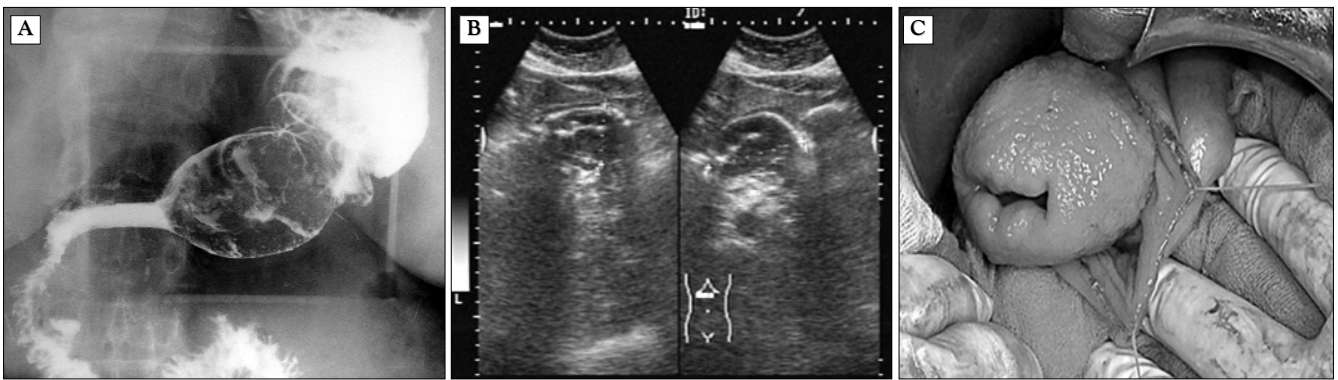


Figure 1. Intra-gastric GIST – radiographic (A), ultrasound (B) and macroscopic (C) aspects.

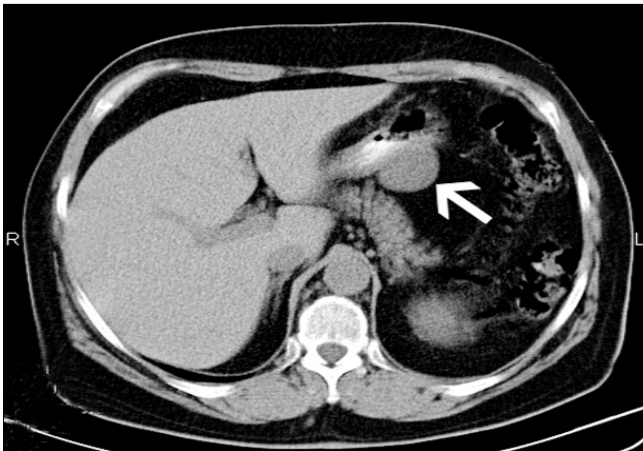


Figure 2. Computer tomography aspect of an extragastric GIST, posterior face



Figure 3. Macroscopic appearance of an extragastric GIST, posterior face



Figure 4. Macroscopic appearance of an extragastric GIST, small curve anterior face



Figure 5. Macroscopic appearance of an extragastric GIST, anterior face

Rectoscopy was suggestive in all cases; biopsy was performed in only 2 cases and it was inconclusive. Abdominoperineal resection was performed in 1 case and anterior resection in 2 cases. The fourth patient was an 82 years old female with a very

low anterior tumor, which categorically refused the abdominoperineal resection, so we were constrained to perform a local excision (Fig. 10).

None of our patients had clinical, imagistic or macroscopic

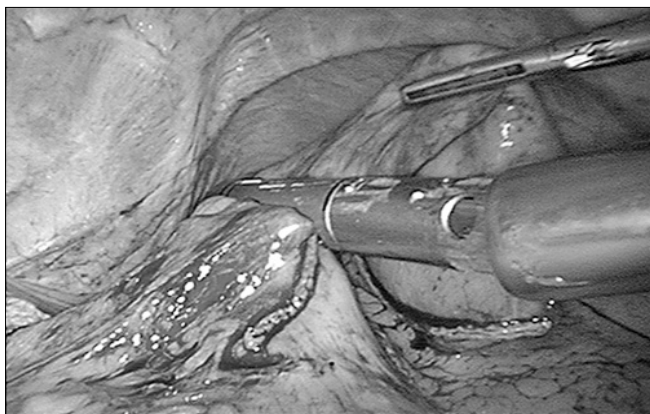


Figure 6. Laparoscopic segmental gastric resection for GIST

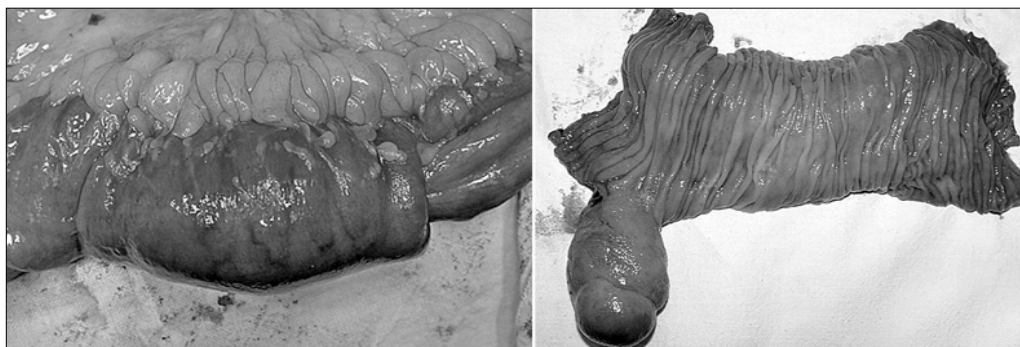


Figure 7. Open surgery segmental gastric resection for GIST

Figure 8. Laparoscopic resection for jejunal GIST



Figure 9. Jejunal intussusception on GIST



metastases. Excepting the patient with local excision of the rectal GIST, all the patients were considered as having gross R0 resections. Pathology report proved that the patient with anterior resection had, in fact, a R1 resection (microscopically positive circumferential margin).

As already mentioned, we had all tissues routinely examined by haematoxylin-eosin stained sections and found that all but 2 patients had spindle cell tumors; the other 2 patients (1 with gastric and the other with rectal tumor) had epithelioid, respectively mixed cellularity.

The patient prognosis based on the consensus approach defined by Fletcher et al. (12) is presented in Table 1.

Postoperatively, 4 patients received Imatinib therapy: 2 patients with intermediate risk gastric GISTs, 1 patient with

perforated jejunal tumor (multiple GISTs and Recklinghouse disease) and the patient with high risk rectal GIST treated by abdomino-perineal resection.

The follow-up period is short (range 8-58 months), but we already have 2 recurrences: the rectal tumor patient that was local excised (local recurrence after 25 months, death after 32 months) and an intermediate risk rectal tumor patient with anterior resection (pelvic recurrence and hepatic metastases after 10 months). Imatinib therapy was started only in the anterior resection patient, after the pathology report proved that it had a R1 resection. The patient has partial response after 3 months of therapy.

The rest of our patients are tumor-free and subjects of a prospective follow-up.

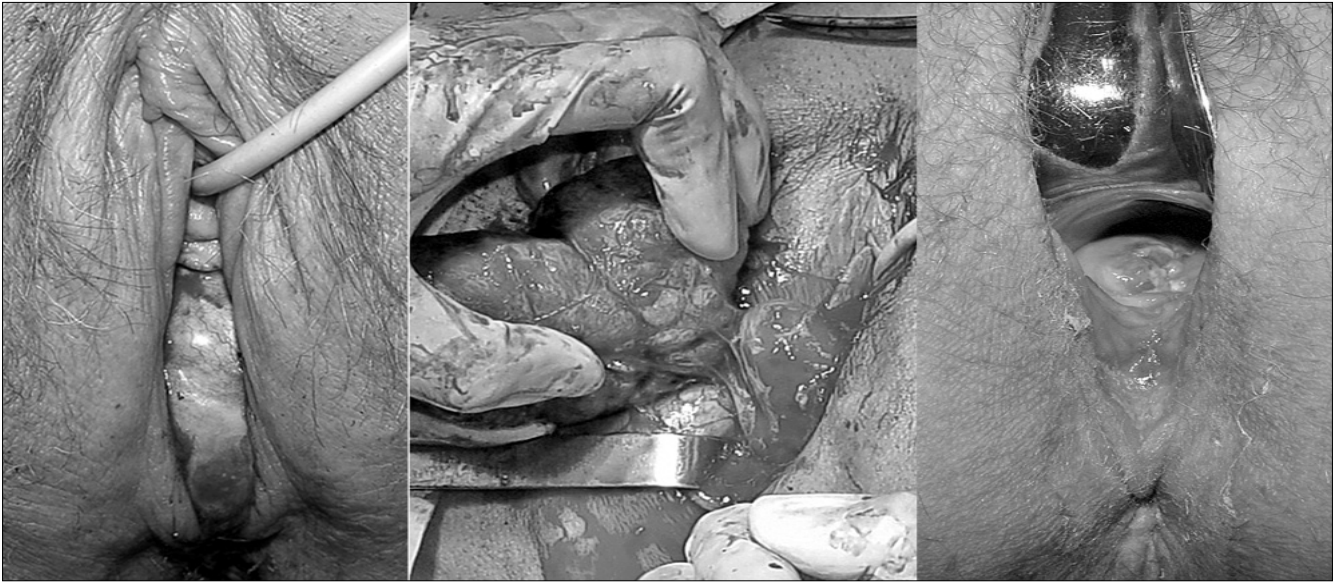


Figure 10. Local excision for low rectal GIST

Discussion

Gastrointestinal stromal tumor is the most frequent mesenchymal neoplasm of the gastrointestinal tract, but until recently it has been an obscure disease (16). Its first definition stated by Mazur and Clark (1) in 1983 was quite vague, based only on histopathological characters in routinely prepared light microscopy specimens. The major breakthrough happened in 1998, when Hirota and his colleagues discovered the c-kit proto-oncogene mutations in these tumors (3); using the expression of c-KIT (CD117) in the tumor cells to define GISTs was the next obvious step.

Our experience in treating non-epithelial tumors of the gastrointestinal tract is much more extensive, but it is only since 2004 that immunohistochemical stain for CD117 became available in "St. Spiridon" University Hospital. All new cases are studied as they are diagnosed, concerning the clinical characteristics, type of surgery, pathologic findings, adjuvant treatment, and recurrence; a prospective study is underway.

Unlike the data in the literature, we have a slight female predominance (61.11%); the median age at the time of diagnosis, the age range and the distribution along the digestive tract are within the limits of other studies.

Our patients were all symptomatic at diagnosis and tumor size was in the range of 1.5-12 cm. Median age at the time of diagnosis was 60 years (range 42-77 years). Location of the tumor was gastric (8 patients - 44.44%), duodenal (2 patients - 11.11%), jejunal (3 patients - 16.67%), right colon (1 patient - 5.55%) and rectal (4 cases - 22.22%).

In the last decade, there was a great interest in this tumor because it has a rather unique tumor biology compared with most other solid tumors in that they are often highly reliant on a single pathway (the KIT receptor tyrosine kinase pathway) for neoplastic growth (17-18).

GISTs frequently harbor gain-of-function mutations in the c-KIT gene. In normal cells activation of the receptor only occurs after binding of the corresponding ligand while gain-of-function mutations result in a constitutively active receptor without the normally required ligand binding (19). The gain-of-function mutations in the c-KIT gene can occur at various sites, the most frequent one being in exon 11 (almost all of GIST lesions arising in the stomach); with a much rare frequency there are found mutations in exons 9, 13, and 17 (predominantly encountered in primary GISTs of the small intestine) (20). Not all GISTs express c-KIT mutations. In the small number of tumors without mutated c-KIT, activating mutations in the PDGFRA gene are found, which induces

Table 1. The patient prognosis based on the consensus approach defined by Fletcher et al. (12)

Tumor site	Malignant potential			
	Very low ¹	Low ²	Intermediate ³	High-risk ⁴
Gastric	2	4	2	0
Duodenal	2	0	0	0
Jejunal	0	3	0	0
Colic	0	1	0	0
Rectal	0	1	2	1

¹tumor < 2cm and < 5 mitoses/50 HPF; ²tumor 2-5 cm and < 5 mitoses/50 HPF; ³tumor < 5 cm with 6-10 mitoses/50 HPF or tumor 5-10 cm with < 5 mitoses/50 HPF; ⁴tumor > 5 cm with > 5 mitoses/50 HPF or tumor > 10cm with any mitoses or any size of tumor with > 10 mitoses/50 HPF.

activation of the same signal transduction pathways as gain-of-function mutations in c-KIT.

Surgical resection with tumor-free margin is considered the right treatment of localized GISTs. Lymphatic spreading has no proven role in GISTs, so resection should be limited to the minimum extent that ensures R0 resection. Although published series present about 10% metastatic disease at diagnose (21-23), we had no such cases, probably due to the small number of cases.

The size of the tumor and the number of mitoses are considered important prognostic factors and are used in defining the so-called Fletcher index (12). Another important prognostic factor is the completeness of the resection. Our recurrences appeared in 2 patients with R1 resection, one with intermediate and the other one with high grade GIST.

The development of the tyrosine kinase inhibitor imatinib, which targets both KIT and PDGFRA, considerably improved the outcome of patients with advanced GIST, but also led to important steps in the understanding of mechanisms underlying numerous cellular processes and their deregulation in cancer (2). Among the 4 patients treated postoperatively with imatinib, only 1 developed local recurrence and hepatic metastases that show a partial response after 3 months of therapy.

Conclusion

Since 2004, we started a prospective study of GIST and we present the first 5 years experience. The complete resection R0 and the malignant potential according to Fletcher index are the most significant prognostic factors. Imatinib treatment may improve outcome in incomplete resected or high risk GISTs.

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