Gastrointestinal stromal tumours.
Our experience ten years later

Ann. Ital. Chir., 2011 82: 267-272

Gloria Ferrocci, Camilla Rossi, Stefano Bolzon, Laura Della Chiesa, Daniela Tartarini, Federico Zanzi, Enzo Durante, Gianfranco Azzena

**Istituto di Chirurgia Generale, Az. Ospedaliero-Universitaria Arcispedale Sant'Anna, Ferrara, Italy*
***U.O. di Chirurgia Generale, Ospedale Santa Maria delle Croci, Ravenna, Italy*

Gastrointestinal stromal tumours. Our experience ten years later

AIM: *To analyze GISTs behaviour observing their clinical evolution and outline the best approach to this neoplasia.*
MATERIAL OF STUDY: *In a period between December 1999 and October 2009 came to our observation, at the Institute of General Surgery, 37 patients with GIST. We conducted a retrospective study evaluating the anatomo-pathological aspects, the clinical situation and the tumour characteristics of the 37 patients with GIST.*
RESULTS: *The 37 patients included 21 women (57%) and 16 men (43%), the mean age was 67 years. GISTs originated from the stomach (27), jejunum (5), ileum (3), anus (1) and transverse mesocolon (1), the symptom most frequently found was acute anaemia and in 5 cases the diagnosis was occasional; 36 patients underwent surgical treatment. Based on tumor size, mitotic count, presence of areas of necrosis and/or haemorrhage, GISTs were classified according to the categories of potential high-grade malignancy (13 pts), intermediate grade (8 pts), low grade (16 pts).*
DISCUSSION: *According to international literature, surgery remains the cornerstone of treatment for patients with primary resectable GIST without evidence of metastasis and should also be utilized when surgery has minimal risk of morbidity for the patient. The goal of surgery is complete surgical resection with negative margins (R0). The follow-up for some patients is still ongoing; only 10 patients underwent to adjuvant therapy with Imatinib.*
CONCLUSIONS: *In the last decade, GISTs have become an emblematic example of the possibility of pharmacologically interfering with the molecular mechanisms of carcinogenesis.*

KEYWORDS: Gastrointestinal stromal tumours (GISTs), Imatinib Mesylate, Surgery.

Introduction

Gastro-intestinal stromal tumours (GISTs) are neoplasia originating from the stromal tissue of the digestive tract and represent the most common subgroup of non-epithelial primary tumours of the gastro-intestinal system (GIMT) [1]. Although quite rare, they are the 0.1-3% of all digestive tract cancers [2]. Their clinical and histological placement is, however, recently acquired because the definition of these tumours has been, for a long time, the subject of disputes and debates. In fact, the GISTs are currently still quite heterogeneous regarding biological behaviour, histogenesis, diagnostic criteria and prognostic factors.

Most of GISTs, by immunohistochemistry, is positive for the expression of surface antigens CD34 and CD117 (or c-kit tyrosine kinase transmembrane receptor for stem cells and mast cells growth factor) which represents the most specific marker of these tumours [3].

In fact, 60-70% of GISTs have proto-oncogene c-kit mutations, therefore causing a permanent activation of the receptor itself resulting in abnormal cellular responses [4].

Pervenuto in Redazione: Dicembre 2010. Accettato per la pubblicazione Gennaio 2011
Correspondence to: Gloria Ferrocci, Istituto di Chirurgia Generale, Az. Ospedaliero-Universitaria Arcispedale Sant'Anna, c.so Giovecca 203, 44121 Ferrara, Italy (E-mail:g.ferrocci@ospfe.it)

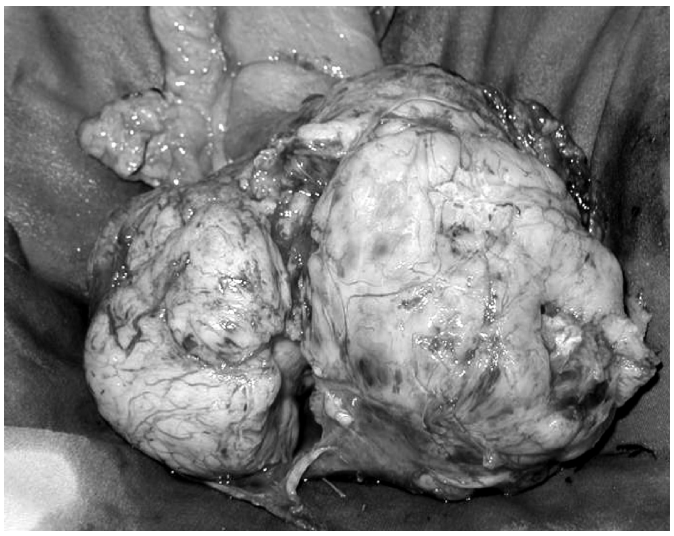

Fig. 1: Gastric GIST.

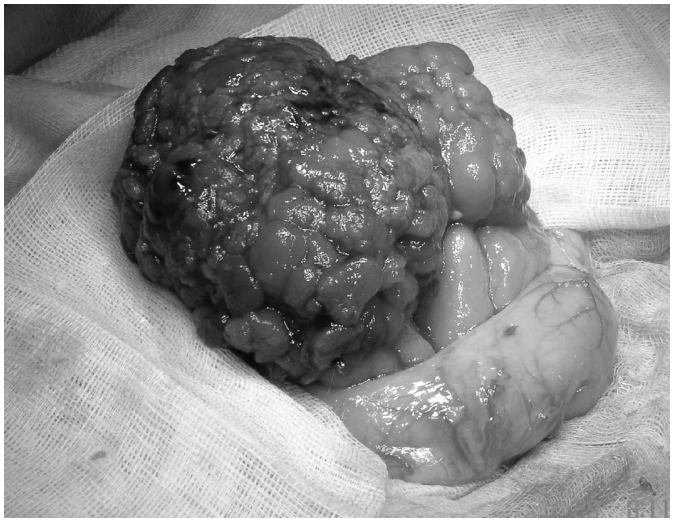

Fig. 2: Gastric GIST.

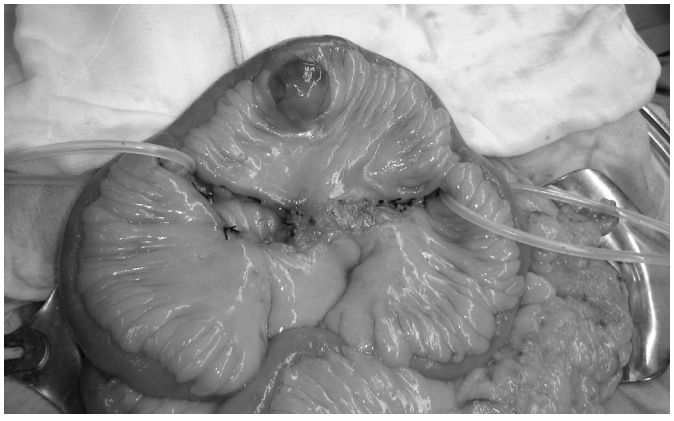

Fig. 3: Ileal GIST.

Recently have been identified other markers which have high diagnostic specificity for GISTs: DOG1 ("Discovered on GIST 1") expressed in 98% of GISTs and PKC q (isoform of PKC family). Based on data of immunohistochemistry and electronic microscopy, it is assumed that GISTs originate from interstitial cells of Cajal (pacemaker cells that control the motility of the entire gastrointestinal tract) or from a common pluripotent mesenchymal precursor [5].

These are typical middle age (50-60 years) tumours, without sex predilection [6]. They originate from the stromal component of the gastrointestinal wall, with predominant localization in the stomach (60-70%), and in small intestine (20-30%); rarely interest other sites (oesophagus, colon-rectum). There are also extra-GI locations (EGISTs) [7].

Clinically, GISTs occur with non-specific symptoms (abdominal pain, feeling of space-occupying mass, nausea and vomiting, anaemia). In 30% of cases they are completely asymptomatic or found accidentally during surgery (acute GI bleeding, intestinal occlusion) [8].

GISTs tend to recur locally and spread via blood (liver metastasis and peritoneal dissemination). Rare cases of lymph node metastasis or in other distant sites (lung, bone, soft tissue) are described. It is hard to make a diagnosis based on non-specific clinical data. In fact, a preoperative diagnosis of GISTs is possible only in 55-65% of cases.

The pre-diagnostic studies of GISTs are similar to those of other tumors of the GI tract (ultrasonography, digestive system radiology with contrast media, endoscopy). However, these investigations are often not diagnostic, because GISTs developing in the submucosa, do not make themselves immediately apparent at the endoscopic exam; the small intestine location makes it even more harduous to identify, due to the difficulty studying this section of the digestive system [9].

The histological pre-operative definition of suspicious lesions helps in treatment planning. However, GISTs are often diagnosed only after histologic examination of a sample removed, because most pathologists have a limited experience in the recognition of these lesions [10].

Although GISTs are the most frequent GI stromal tumor, a large number of lesions should be considered in the differential diagnosis, including mesenchymal, nervous and endocrine GI tract tumours [8]. GISTs represent a spettrum continuum of cancers regarding the biological behaviour (low, intermediate and high risk of malignant potential) [11]. There are no prognostic parameters to define with absolute certainty the malignant potential of these tumours. However, the most important prognostic factors are: tumor size (> 5 cm), mitotic index (> 5 / 10 HPF), tumor site (small bowel vs. stomach), high cellularity, aneuploidy, c-kit mutations, areas of necrosis / haemorrhage, distant metastasis and peritoneal dissemination [12].

Surgical resection is the first-line treatment for primary GISTs localized (non metastatic), for which is still pos-

sible the radical excision of the primary tumour in absence of remote metastasis. Surgical treatment is made in about 85% of patients, being these tumors resistant to radiotherapy and chemotherapy [13].
The ideal surgical procedure should aim to perform a complete cancer resection (R0: no residual microscopic tumor) with histologically negative margins [14].
The advent of molecular targeted therapy with Imatinib Mesylate has markedly changed the clinical approach to GISTs and, in particular, has revolutionized the treatment of patients with advanced or metastatic or inoperable disease [15].
Considering its effectiveness (objective response around 70%) and the high risk of recurrence after resection of the primary lesion, Imatinib has been evaluated in adjuvant therapy after surgical resection of primary GIST, and in this context would be the ideal treatment. Another area of application is the use of Imatinib as a neoadjuvant approach (or pre-surgical) [16].
Nowadays new second-generation molecules are available (Sunitinib or SU11248, Everolimus RAD001) to use in case of appearance of resistance to Imatinib or serious side effects [17].

Materials and methods

Thirty-seven patients with gastrointestinal stromal tumour (GIST) were retrieved from the archives of General Surgery Institute of the Arcispedale S.Anna in Ferrara and the General Surgery Department of the Hospital S. Maria delle Croci in Ravenna, between 1999 and 2009.
21 patients were females (57%) and 16 were males (43%) with a ratio M:F of 1:1,3.
The median age was 67 years (respectively 70 years for women and 63 for men).
Clinically the most frequent symptom was acute anaemia (10 pts 27 %) due to a gastrointestinal bleeding (2 pts 22%). Other observed symptoms were: abdominal colic pain (4 pts 11 %), epigastric pain (7 pts 19%), discomfort feeling (8 pts 22%) and proctalgia (1 pt 3%). GISTs resulted entirely as an occasional finding in 5 patients (14%).
In this study were included all the patients with preoperative and postoperative GIST anatomo-pathologic diagnosis.
A preoperative diagnosis was achieved only in 4 patients (11%) through EGDS biopsy (1 case 3%) and Ultrasonographic biopsy (3 cases 8%) subsequently confirmed by the histopathologic definitive examination performed on the operative specimen. In another case a diagnostic suspect of GIST was set through endoscopic ultrasonography (EUS).
An histopathologic intraoperative examination was made on a surgical specimen in 7 cases (19%): in 6 cases (16%) the pathological GIST diagnosis was confirmed in the definitive histopathologic examination, while in one case (3%) the intra-operative diagnosis (neuroendocrin tumour metastasis) was different from the definitive.

TABLE I - *Anatomo-pathological aspects and surgical treatment of GISTs.*

	Stomach (26)	**Ileum** (3)	**Jejunum** (5)	**Anus** (1)	**Mesocolon** (1)	**Total** (36)*
Tumor size						
>5 cm	11	3	1	0	1	16
<5 cm	15	0	4	1	0	20
Mitotic count						
> 5 mitoses/ 50 hpf	10	3	0	0	1	14
< 5 mitoses/ 50 hpf	16	0	5	1	0	22
Type of resection						
– tumorous excision	10	0	1	1	1	13
– partial gastrectomy	8	0	0	0	0	8
– total gastrectomy	4	0	0	0	0	4
– gastrectomy and splenectomy	2	0	0	0	0	2
– "en bloc" resection	2	0	0	0	0	2
– small bowel segmentary resection	0	3	4	0	0	7
Malignant potential						
– higt risk	8	3	0	0	1	12
– intermedie risk	6	0	2	0	0	8
– low risk	12	0	3	1	0	16

* Data on 36 pts because 1 pt did not undergo to surgical treatment.

In 28 cases (76%) GIST diagnosis was obtained only by histopathological examination performed on the surgical removed specimen. In one case the diagnosis was obtained by endoscopic biopsy but the patient was not operated because of the poor clinical conditions.
We considered morphological and immunohistochemical tumours characteristics, anatomical site, neoplasia size, necrotic areas in the context of the tumour and adjacent structures infiltration. Particularly the immunohistochemical analysis investigated the positiveness for the specific surface markers as CD117 - cKit, CD 34, but also protein S-100, smooth muscle actina (SMA), vimentina, desmina.
The mitotic index was evaluated through the mitosis number on 50 fields to tall enlargement (High Power Fields). The proliferation index determined in that way mirrors the proportion of cells in active growth phase.
All the patients underwent to surgery, except one, treated with molecular therapy because of his general conditions.
The surgical technique was chosen considering the lesion site and size. Therefore different interventions were performed: tumorous excision (13 pts 36%), partial gastrectomy (8 pts 22%), total gastrectomy (4 pts 11%), gastrectomy and splenectomy (2 pts 6%), "en bloc" resection (2 pts 6%) and small bowel segmentary resection (7 pts 19%).

Results

We have conducted a retrospective study appraising the anatomo-pathological aspects, the tumour characteristics, the clinical condition and the therapy of the patients. The clinical data were obtained by the hospital case sheet of the patients, as the data related to the follow-up. Clinical, pathological and therapeutical characteristics were analyzed, and their relationship with recurrence, mortality and molecular therapy.
The risk of malignancy (high, intermediate and low risk) has been determined considering the tumour size, the mitotic count and the necrotic areas.
Concerning the anatomical location in our patients, the GISTs appeared in the stomach (27 pts 73%), jejunum (5 pts 14%), ileum (3 pts 8%), anus (1 pt 3%) and mesocolon (1 pt 3%).
We have considered different parameters to try to define a prognosis or to ascribe a predictive value to the biological behaviour of these tumours, but such criterions are still vague and not able to discriminate among benign and malignant lesions.
We have regarded the following parameters: tumor size (> 5 cms), mitotic index (n° of mitosis for HPF: > 5/50HPF), location (gastric vs intestinal), local extension (infiltration of adjacent structures/organs), areas of necrosis/haemorrhage, metastasis and peritoneal dissemination and reactivity for CD34/CD117.

TABLE II - *Patient demographics and presentation.*

Age (years)	
Median	67 (35-82)
Gender	
Male: Female	16: 21
Clinical presentation	
Anaemia	10 (27%)
Gastrointestinal bleeding	8 (22%)
Pain/discomfort	8 (22%)
Epigastric pain	7 (19%)
Syncope	6 (16%)
Melena	6 (16%)
Occasional	5 (14%)
Abdominal colic	4 (11%)
Hematemesis	3 (8%)
Vomiting	1 (3%)
Constipation	1 (3%)
Proctalgia	1 (3%)
Dysphagia	1 (3%)
Hyperpyrexia	1 (3%)

The middle dimension of the identified tumours was of 6,8 cms, with a variable range from 1,5 cms to 23 cms. The mitotic index was > 5/50 HPFs in 15 cases (41%) and < 5/50 HPFs in 22 cases (59%).
Areas of necrosis were present in 6 cases (17%) and the immunohistochemical analysis have underlined a reactivity for CD117 (36 cases, 97%) and CD34 (30 cases, 81%).
Based on tumour size, mitotic index, presence of areas of necrosis or haemorrhage, the GISTs have been classified in different malignant potential: high risk (13 pts 35%), intermediate risk (8 cases 22%), low risk (16 pts 43%).
In four cases (11%) we have underlined, during surgery, the presence of omentum, visceral-parietal peritoneum and liver metastasis resulted compatible with GIST metastasis. In all these cases it has dealt with GISTs already of great dimensions (middle diameter of 13 cms) at the diagnosis. In 2 patients the GIST metastasis appeared two years after the surgical complete removal of the neoplasia. In one case it has dealt with peritoneal and liver metastasis in a patient who had suspended Imatinib therapy 2 years before because of intolerance and in a case there has been peritoneal metastasis in a patient who had never taken Imatinib.
Among all these patients with GIST diagnosis, ten have been submitted to molecular therapy with Imatinib, four of which had metastasis at the diagnosis or recurrence. Of these, 8 had a GIST with high malignant potential risk and 2 with low malignant potential risk. Only one patient has been treated with molecular therapy without undergoing a surgical intervention for the poor clinical conditions.

Two patients underwent to surgical treatment (total gastrectomy and "en bloc" resection) and they had a local recurrence and a resistance to Imatinib therapy. For these reasons they were enlisted in an experimental protocol with new generation drugs (Sunitinib); one patient died later for the progression of the illness.
The patient with GIST of the anus had a recurrence one year after the surgery and so she has begun the therapy with Imatinib that has maintained the illness stable.
The patient with GIST of the mesocolon underwent to an intervention of exeresis of the abdominal mass refusing herself to begin a molecular therapy. Two years later appeared peritoneal metastasis, that had required a second surgical intervention and the beginning of the molecular therapy.
No patients have been submitted to neoadjuvant therapy.
Six deaths (16%) had occurred: in 4 cases the reason of the death was correlated to the progression of the illness after surgery, in a case such advance has happened for therapy molecular resistance and in a case such progression has taken place for therapy molecular resistance in a patient who had not been submitted to surgical intervention.

Discussion

Diagnostic methods employed for small size GIST (<2 cm) include endoscopy and endoscopic ultrasonography. In tumours > 2 cm, diagnostic procedures include a CT scan, along with endoscopic or percutaneous biopsy. In cases when an abdominal nodule is not amenable to endoscopic evaluation, laparoscopic/laparotomic excision should be considered.
Surgery remains the cornerstone of treatment for patients with primary respectable GIST without evidence of metastasis and should also be utilized when surgery has minimal risk of morbidity for the patient. The goal of surgery is complete surgical resection with negative margins (R0).
A radical excision of a primary localized GIST is correlated to 40%-55% DSF (Disease Free Survival) at 5 years.
Risk of recurrence in primary GIST has been associated with size, mitotic rate and tumour location.
For patients with marginally respectable GIST due to size or poor positioning, or for whom R0 surgery is not feasible, neoadjuvant Imatinib therapy should be considered to avoid or reduce the risk of bleeding and the tumour rupture. Maximal tumour response to Imatinib should be achieved (6-12 months) before surgery is performed.
Adjuvant Imatinib has been associated with improved RFS (Recurrence Free Survival); however, the optimal duration of therapy remains to be determined.
In adjuvant treatment the standard dose of Imatinib is 400 mg/day; in case of disease progression could be approached a dose-escalation (800 mg/day).
After disease progression using Imatinib or resistance/intolerance to Imatinib is possible to adopt second generation molecular therapy, as Sunitinib.

Conclusions

Pre-operative diagnostic studies are difficult and non-specific; making a surgical excision of the lesion is the only way to obtain a histologic diagnosis.
The role of surgery in metastatic GISTs remains unclear. Imatinib has changed the natural history of metastatic GISTs. In a proportion of patients with initially unresectable disease, Imatinib treatment may now enable surgical resection.
We believe that surgical resection should be explored at every stage in the natural history of metastatic GISTs. Close liaison between oncology, radiology and the surgical teams is essential for diagnosis, treatment and follow-up.
Each case should undergo careful ongoing review by a multidisciplinary team which has the experience of managing these rare tumours. Surgical resection, when feasible, is likely to provide the best treatment and may potentially eliminate resistant clones.
Summarizing our results with the influence of tumour size and mitotic count on the DFS, we support the concept that all patients with high risk GIST, metastatic or non-operable disease need to be assessed for adjuvant treatment with Imatinib.

Riassunto

I GISTs sono neoplasie mesenchimali originanti dal tessuto stromale del tratto gastrointestinale. Costituiscono lo 0.1-3% di tutte le neoplasie del tubo digerente e sono localizzati principalmente a livello dello stomaco. Sono tumori tipici dell'età medio-avanzata, senza apparente predilezione di sesso. I markers più caratteristici sono costituiti dagli antigeni di superficie CD117 e CD34, espressi nella maggior parte dei GISTs.
Abbiamo condotto uno studio retrospettivo di un periodo di dieci anni compreso tra il 1999 e il 2009, valutando gli aspetti anatomo-patologici, le caratteristiche tumorali, il quadro clinico ed il percorso terapeutico intrapreso da 37 pazienti giunti alla nostra osservazione con diagnosi di GIST, ponendo tali dati in relazione all'outcome in termini di comparsa di recidive e mortalità. I pazienti, 21 donne (57%) e 16 uomini (43%), con un'età media di 67 anni al momento della diagnosi, sono stati tutti sottoposti ad intervento chirurgico ad eccezione di uno a causa delle scadenti condizioni cliniche. La sede principalmente interessata è risultata essere lo stomaco (72%). La sintomatologia di più frequente riscontro è stata un quadro di anemizzazione acuta (27%), dovuta spesso ad un quadro di emorragia

gastrointestinale (22%), tuttavia in 5 casi la diagnosi è stata occasionale, confermando le problematiche per una diagnosi precoce legate alla aspecificità e variabilità della sintomatologia. Le analisi immunoistochimiche hanno evidenziato una reattività per CD117 nel 97% dei casi. In base alla dimensione tumorale, alla conta mitotica, alla presenza di aree di necrosi e/o di emorragia, i GISTs sono stati classificati secondo le categorie del potenziale di malignità: ad alto grado (13 casi), grado intermedio (8 casi), basso grado (16 casi). Dieci pazienti (27%) hanno intrapreso una terapia molecolare con Imatinib (compreso il paziente non sottoposto ad intervento chirurgico). Di questi, 8 pazienti presentavano un GIST ad alto grado di malignità (di cui due recidivi e uno metastatico) e 2 pazienti un GIST a basso grado di malignità (di cui una recidiva). Nessun paziente è stato sottoposto a terapia molecolare neoadiuvante. Al termine del nostro studio abbiamo osservato 6 decessi in totale (16%), di cui 4 correlati alla progressione della malattia.

In conclusione, la diagnosi preoperatoria di GIST risulta notevolmente problematica a causa della variabilità e dell'aspecificità della sintomatologia di presentazione. La terapia chirurgica rappresenta al momento la prima scelta soprattutto per la malattia localizzata; controverso rimane il ruolo della chirurgia nel trattamento delle metastasi.

Nell'ultimo decennio i GISTs sono divenuti un esempio emblematico della possibilità di interferire farmacologicamente con i meccanismi molecolari della cancerogenesi; l'introduzione della terapia molecolare specifica con Imatinib Mesylato (Glivec) ha portato a risultati molto soddisfacenti nei casi di malattia avanzata, recidiva e ad alto potenziale di malignità.

References

1) Strickland L, Leston GD, Muro-Cacho CA: *Gastrointestinal stromal tumors.* Cancer Control, 2001; 8:252-61.

2) Ismail I, Sacco S, Navarra GG, Bonomi S, Galluzzo V, Virzì S: *Gastrointestinal stromal tumors: A study of nine cases.* Osp Ital Chir, 2003; 9:401-08.

3) Lattarulo S, Ugenti I, Ferrarese F, Fabiano G: *Tumori stromali gastrointestinali: Attuali problematiche.* Chir Ital, 2003; 55:219-24.

4) Joensuu H, Fletcher C, Dimitrijevic S, Silberman S, Roberts P, Demetri G: *Management of malignant gastrointestinal stromal tumors.* Lancet Oncol, 2002; 3:655-64.

5) Sabah M, Leader M, Kay E: *Gastrointestinal stromal tumours: An update.* Current Diagnostic Pathology, 2005; 11:400-10.

6) Casper ES: *Gastrointestinal stromal tumors.* Curr Treat Options Oncol, 2002; 3:267-73.

7) Joensuu H: *Current perspectives on the epidemiology of gastrointestinal stromal tumors.* EJC Supplements, 2006; 4:4-9.

8) De Silva Mvc, Reid R: *Gastrointestinal Stromal Tumors (GISTs): C-KIT mutations, CD117 expression, differential diagnosis and target cancer therapy with Imatinib.* Path Oncol Research, 2003; 9:13-19.

9) Sturgeon C, Chejfic G, Espat NJ: *Gastrointestinal stromal tumors: A spectrum disease.* Surg. Oncol., 2003; 12: 21-26.

10) Van Der Zwan SM, Dematteo RP: *Gastrointestinal Stromal Tumors: 5 years later.* Cancer, 2005; 104:1781-88.

11) Peperini N, Maturo A: *Gastrointestinal stromal tumors: Problemi aperti.* Giorn It Oncol, 2002; 22:135-37.

12) Nilsson B, Bùmming P, Meis-Kindblom Jm, Odèn A, Dortok A, Gustavsson B, Sablinska K, Kindblom LG: *Gastrointestinal stromal tumors: The incidence, prevalence, clinical course and prognostication in the preImatinib mesylato era.* Cancer, 2005; 103:821-29.

13) Castronovo G, Ciulla A, Tomasello G, Urso G, Damiani S: *Considerazioni cliniche sui tumori gastrointestinali stromali.* Ann Ital Chir, 2003; 74:523-27.

14) Connolly EM, Gaffney E, Reynolds JV: *Gastrointestinal stromal tumors.* Brit Journ Surg, 2003; 90:1178-86.

15) Des Guetz G, De Mestier P: *Finalmente un trattamento efficace nei sarcoma digestive indifferenziati (tumori stromali).* J Chir, 2002; 139:268-73.

16) Heinrich MC: *Molecular basis for treatment of gastrointestinal stromal tumours.* EJC Supplements, 2006; 4:10-18.

17) Reichardt P, Schneider U, Stroszczynski C, Pink D, Hohenberger P: *Molecular response of gastrointestinal stromal tumour after treatment with tyrosine kinase inhibitor Imatinib mesylato.* Journal of Clinical Pathology, 2004; 57:215-17.