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Surgical Management of Gastrointestinal Stromal Tumours: A Large Single Centre Experience

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Abstract

Introduction: Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract, accounting for 1-3% of all gastrointestinal malignancies. The most common site of origin within the gastrointestinal tract is the stomach, followed by the small bowel. The clinical presentations of GISTs are highly variable according to the site of origin and the and size, but none of them is pathognomonic. GISTs are indeed often diagnosed incidentally during investigations performed for other reasons. The preoperative radiological diagnosis of GISTs is complicated by their varied macroscopic morphology. Moreover, the precision of preoperative histopathological diagnostics is reduced by the submucosal localization of the lesion. Surgical resections is the 'gold standard' therapeutic choice of primary GISTs. Recently, a targeted therapy with inhibitors of tyrosine kinase receptors (imatinib) has been introduced for the management of advanced and metastatic tumors.

Aim of the study: The present study was designed in order to assess the survival of GIST-diagnosed patients after surgical resection, to identify factors that could have a prognostic impact and finally evaluate the role of Imatinibmesylate as therapeutic option in this group of individuals.

Materials and methods: We retrospectively collected 88 consecutive patients who were diagnosed with GIST and surgically resected in our center (Department of General Surgery, 'San Matteo' Hospital, Pavia) in the last 15 years (January 2000-December 2014). General and clinical data were reviewed from patients' medical reports: symptoms at presentation, clinical course, histopathological features, type of surgery, post-surgical complications and disease-free survival.

Results: 45 (51.13%) out of 88 patients were male, 43 (48.86%) were female. The median age of our study

population was 55 years. Most tumors originated in the stomach (63.63%, 56), 22.72% (20) were isolated from the small intestine, duodenum (3.4%, 3), colon (3.4%, 3), esophagus (2.27%, 2) or elsewhere (4.54%, 4) with an average diameter of 9.1 cm (range 0.5-19 cm). Tumor size was less than 2.0 cm in 22.72% (20) of patients, between 2.0 and 5.0 cm in 38.63% (34) of patients, between 5.0 and 10.0 cm in 25% (22) of patients, and greater than 10.0 cm in 13.63% (12). Twenty-one patients presented with gastrointestinal bleeding (23.86%), 17 patients with intestinal obstruction (19.3%), 8 with intraperitoneal haemorrhage (9.09%) and 4 with perforation and peritonitis (4.5%). Thirty-eight patients were asymptomatic (43.01%) and diagnosed incidentally during investigations performed for other reasons. Complete macroscopic resection (Wedge+Partial organ resection) was performed in 74 patients (84.1%), total organ resection and peritoneal biopsy were chosen for 9 patients (10.22%), while 5 patients (5.685) received "en-bloc" resection. Fourty-six (52.27%) out of 88 patients underwent postoperative (adjuvant) treatment with Imatinib and only one isolated case received a combination of Imatinib and Sunitinib. 23 (26.14%) patients did not need any adjuvant therapy but only a close follow up with Computed Tomography (CT) and blood tests monitoring every 3/6 months. We were not able to collect data from 18 (20.45%) patients who did not presented at the follow-up visits.

Conclusion: GISTs constitute an interesting chapter of oncological pathologies. Surgery is still the gold standard treatment in localized primary GIST. Still a little number of cases with low risk disease can be treated with radical surgery. The prognosis is strictly related to the size and completeness of the surgical resection. Large size, high mitotic rate, high risk group, and adjacent organ involvement all contribute to bad outcome of GISTs. Imatinib therapy significantly improves survival of patients with intermediate-high risk or advanced staging.

Keywords: Gastrointestinal Stromal Tumors; Imatinib; Surgery

Introduction

Gastrointestinal Stromal Tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal (GI) tract [1]. Currently, they are recognized and classified as distinct entities from other neoplasms of the connective tissue, with specific clinical and histopathological features. Although the majority of them is small in size, their diameter can vary from 1 to 20 cm. Metastasis occur mostly in the abdominal cavity and liver. The nodal involvement is less frequent: either pulmonary or extra-abdominal lymph-nodes metastasis have an extremely low incidence in comparison to what happens for epithelial neoplasms [1-3]. The reported annual incidence is about 10-20 cases to 1 million of individuals [2]. These tumors occur at any time during life, but the median age at diagnosis has been reported to be 55-60 years [3], affecting males and females at the same rate. Although they most commonly occur in the stomach (50-70% of cases), followed by

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the small intestine (20-30% of cases) and duodenum 5% [4,5], GISTs are found throughout the GI tract. Locations such as the esophagus, the colon and the rectum account for less than 10% of all cases [4,5]. Uncommonly, they can also arise within the greater omentum, appendix and gallbladder. The interstitial cells of Cajal, pluripotent intestinal pacemaker cells, were identified as the origin of GISTs [6]. A gain-of-function sporadic mutation within the tyrosine kinase receptor's gene plays a fundamental role in their pathogenesis, being responsible for the deregulation of processes involved in the cell cycle control, thus leading to cell hyper-proliferation [7]. Tyrosine kinase receptor (C-KIT) is a transmembrane receptor that is activated by the binding of KIT protein, a C-KIT proto-oncogene product. Up to 80% of GISTs have KIT protein mutations, while 8% have mutations in the Platelet derived growth factor receptor a (PDGFRa), a-polypeptide gene encoding a C-KIT homologous type III receptor tyrosine kinase protein [8]. The essential ligand-independent activation of the mutated KIT protein results into imbalance between cell survival and proliferation, overcoming the natural process of programmed cell death [9]. GISTs specific immunohistochemical markers are CD117 (95% positivity), CD34 (70-80% positivity), Smooth Muscle Actin (20-30% positivity), and Desmin (<5% positivity) [10].

GISTs are frequently asymptomatic until advanged stages. Small tumors are usually incidental findings during surgical, endoscopic or radiological investigations for other reasons. There are no pathognomonic symptoms and for this reason a high-level of suspicion for GISTs should be kept during the diagnostic work-up of patients presenting with GI bleeding, intestinal obstruction, intra-peritoneal hemorrhage or peritonitis. The most frequent signs are anemia, weight loss and bleeding. Symptoms are mainly abdominal pain and mass-related effects. Patients may complicate with acute abdomen, obstruction, perforation and eventually peritonitis. Other presentations include nausea, vomiting, and abdominal distention [3]. GISTs present a varied of morphological appearances and this feature may further complicate their pre-operative diagnosis through imaging. Their histopathological determination may result cumbersome due to possible submucosal localizations, reducing the accuracy and reliability of bioptic procedures. Ultrasound endoscopy is the first step of the diagnostic workup, followed by cross-sectional imaging techniques such as Computed Tomography (CT) and/or magnetic resonance imaging (MRI). There are several criteria for risk stratification, Fletcher's criteria is the first attempt in assessing the malignant potential of GISTs. The parameters determining risk stratification are mainly two: tumor size and mitotic activity. According Miettinen and Lasota the criteria for risk stratification are mainly three: tumor size, mitotic count and tumor location [11-13].

Surgical resection remains the gold-standard procedure for an efficacious treatment of very-low and low risk disease, while the additional use of oral inhibitors like Imatinib Mesylate (trade name: Gleevec, Glivec) is considered in patients with unresectable or metastatic disease [14]. Conventional chemotherapy and radiotherapy are usually ineffective [15,16]. Imatinib Mesylate belongs to a class of chemotherapeutic agents that act as specific inhibitors of a number of tyrosine kinase enzymes, linked to the C-KIT receptor. More specifically, it blocks the kinase activity of the mutated polypeptide codified by the C-KIT proto-oncogene (CD117) involved in tumor growth. It also has inhibitory activity on mutated PDGF-R (platelet derived growth factor receptor), a well known factor regulating cell proliferation, differentiation, growth and development. Initially introduced as treatment for chronic myeloid leukemia and acute lymphoblastic leukemia, Imatinib was later approved in 2001 as therapeutic option in metastatic GISTs [17,18]. The starting recommended dose is 400 mg per day, to be increased up to 800 mg in case of resistance or disease progression. The best achievable response is obtained within the first 6-12 months. Therapeutic benefits usually decline after a year of treatment, at this time resistance indeed is as high as 15-20%. Surgery should be considered if any improvement can be observed at CT scan after 6 months of treatment with Imatinib. The ideal surgical moment is after the maximum response and before the onset of resistance. Another chemotherapeutic option is Sunitinib (Sutent), a recently validated drug, designed to work as tyrosine kinase inhibitor applied for the treatment of Imatinib-resistant or-intolerant GISTs. In addition to the inhibition of tyrosine kinase activity, Sunitinib action extends also to the hindrance of the angiogenic activity proper of VEGF (vascular endothelial growth factor) [19-21].

Aim of the Study

The purpose of this retrospective study was to assess the survival after surgical resection and prognostic factors of patients who received a diagnosis of GIST. We also retrospectively evaluated the role of Imatinib Mesylate in affecting the outcome of a group of patients that after surgery needed such a therapy. This article reviews risk stratification in resectable GISTs and illustrates how recent findings may not only improve risk assessment but also indentify who are pontentially most likely to benefit from adjuvant therapy.

Material and Methods

Eighty-eight patients with a confirmed diagnosis of GIST who were admitted to the Surgery Department at the 'San Matteo' Hospital of Pavia between January 2000 and December 2014 were enrolled. Each patient agreed to sign the informed consent. The study received official institutional and ethical approval from the participating institutions. We retrospectively reviewed the medical records and disease-free survival of 88 patients who underwent surgical removal of GISTs. Data on patients' gender, age, clinical presentations, tumor characteristics, histo-pathological features, clinical course, pathological findings, radiological investigations, type of surgical procedure, classification of risk according to Fletcher and Miettinen, treatment with Imatinib Mesylate, number of postoperative recurrencies and overall survival and disease-free survival, intra- and post-operative complications were collected and summarized into three table.

Their clinical presentation is aspecific and highly variable according to their site and size. There are no precise criteria for pre-operative diagnosis because GISTs are frequently asymptomatic until advanged stages, that's why only the symptoms and imaging techniques do not allow us to get a diagnosis. According to Cavaliere et al., [22], the difficulty in having a pre-operative diagnosis comes mainly from the aspecificity of the symptoms and the possibility to have a definitive diagnosis only after performing the pathological, histological and immunological analysis of the excised tumour. Morphological and immunohistochemical examinations of C-KIT expression allow the correct identification of GIST enabling the differential diagnosis with other mesenchymal, neural and neuroendocrine neoplasms occurring in the abdomen. A diameter greater than 2 cm is usually a positive indication for surgical resection, whilst lesion smaller than this threshold are closely monitored for metastasis [23,24]. The prognosis is mainly related to size and completeness of surgical resection but the large size, a high mitotic rate, classification into high-risk group, and adjacent organ involvement are all contributors to a dismal outcome of GISTs. Patients with a GIST's size less than 5 cm had a significantly longer survival than patients with bigger tumors. Katharine et al., [25]

found that tumor size had a significant impact on overall survival. Patient with advanced-stage GISTs usually face severe morbidity and short life-expectancy. It was estimated that 47 (53.41%) out of 88 patients underwent postoperative treatment with Imatinib and only 1 case received a combination of Imatinib and Sunitinib. Twenty-two (25%) patients did not need adjuvant chemotherapeutic support but were recommended for a close follow-up with Computed Tomography (CT) and blood analysis every 3-6 months. All the surgical specimens underwent histopathological examination and immuno-histochemical staining for detection of C-KIT (CD117). Early and late post-operative complications, local and distant recurrence and mortality rates were recorded during the follow-up period.

Patients. n (%)			
Age	< 55 years		35 (39.77%)
	> 55 years		53 (60.22%)
Sex	Male		45 (51.13%)
	Female		43 (48.86%)
Symptom	Asymptomaic		38 (43.1%)
	Gastrointestinal bleeding		21 (23.86%)
	Intestinal obstruction		17 (19.3%)
	Intraperitoneal hemorrhage		8 (9.09%)
	Rupture and peritonitis		4 (4.5%)
Location	Gastric		56 (63.63%)
	Ileum		20 (22.72%)
	Duodenum		3 (3.4%)
	Colon		3 (3.4%)
	Esophagus		2 (2.27%)
	Rectal		(1.13%)
	Liver		(1.13%)
	Pancreatic		(1.13%)
	Spleen		(1.13%)
Tumor size	< 2 cm		20 (22.72%)
	> 2 and < 5 cm		34 (38.63%)
	> 5 and < 10 cm		22 (25%)
	> 10 cm		12 (13.63%)
Mitotic count	< 5/50 HPF		47 (53.40%)
	> 5 and < 10/50 HPF		31 (35.22%)
	> 10/50 HPF		10 (11.36%)
Immunohistochemistry	KIT exon CD117		31 (35.22%)
	KIT exon CD34		6 (6.81%)
	Wild-type		51 (57.95%)
Morphological Type	Spindle cell		48 (54.54%)
	Epithelioid cell		23 (26.13%)
	Mixed cell		17 (19.31%)
Risk according Fletcher	Very low		7 (7.95%)
	Low		30 (34.09%)
	Intermediate		15 (17.04%)
	High		36 (57.95%)
Risk according Miettinen	No risk		13 (14.7%)
	Low		47 (53.40%)
	Intermediate		18 (20.45%)
	High		10 (11.36%)
Type of surgical resection			
Wedge			33 (37.5%)
	Gastric	21 (63.63%)	
	Ileum	7 (21.21%)	
	Duodenal	2 (6.06%)	
	Esophagus	1 (3.03%)	
	Liver	1 (3.03%)	
	Pancreatic	1 (3.03%)	
Partial			41 (46.6%)
	Gastric	22 (53.65%)	
	Ileum	13 (31.70%)	
	Colon	3 (7.31%)	
	Rectal	1 (2.43%)	
	Duodenum	1 (2.43%)	
	Esophagus	1 (2.43%)	
Total			9 (10.22%)
	Gastrectomy	8 (88.88%)	
	Splenectomy	1 (11.11%)	
'En bloc'			5 (5.68%)
	1 Gastrectomy and left liver lobectomy		
	1 Gastrectomy and right liver lobectomy		
	1 Gastrectomy and splenectomy		
	1 Gastric and transverse colon resection		
	1 Gastric. ileum resection and liver biopsy		
HPF = High Power Fields.			

Table 1: Clinico-pathological features.

Results

All the patients enrolled in this study had a definitive diagnosis of GIST assessed post-operatively by an anatomopathologist through morphological, histological and immunohistochemical analysis. In our study, all the patients underwent surgery. The characteristics of the 88 patients are summarized in Table 1. The median age of our study population was 55 years, 51.13% (45) of patients were male. Twenty-one (23.86%) patients presented with gastrointestinal bleeding, 17 (19.3%) with intestinal obstruction, 8 (9.09%) with intraperitoneal hemorrhage and 4 (4.5%) with rupture and peritonitis. Thirty-eight (43.01%) patients were asymptomatic and were diagnosed incidentally during investigations performed for other conditions. Patients presenting hematemesis and/or melena (35, 39.77%) were investigated through upper GI endoscopy followed by bioptic sampling, patients reporting fresh bleeding from the rectum (4, 4.55%) received colonoscopy. Computed tomography (CT) scan of the abdomen and pelvis was performed in all the cases. Most tumors originated in the stomach (63.63%, 56), 20 in the small bowel (22.72%), 3 in the duodenum (3.4%), 3 in the colon (3.4%), 2 in the esophagus (2.27%), and only 1 single case (1.13%) respectively in the rectum, pancreas, liver and spleen. The average size of tumors was 9.1 cm (range 0.5-19 cm). Tumor size was less than 2.0 cm in 22.72% (20) of patients, between 2.0 and 5.0 cm in 38.63% (34) of patients, between 5.0 and 10.0 cm in 25% (22) of patients, and greater than 10.0 cm in 13.63% (12). Mitotic rates were also determined: most tumors (53.40%, 47) had a low mitotic rate (<5/50 HPFs), 35.22% (31) intermediate (>5 but <10/50 HPFs), and 11.36% (10) high (>10/50 HPFs). Immunohistochemistry showed that 31 (35.22%) tumors were positive only for CD117, 6 (6.81%) positive only for CD34, and 51 (57.95%) positive for both CD117/CD34. The 88 patients were classified as follows according to the cells morphology type founded on histologic examination of the surgical specimen: Spindle cell 48 patients (54.54%), Epithelioid 23 (26.13%), mixed 17 (19.31%). Under a clinical point of view, few patients displayed disease complications, more specifically tumor rupture and peritonitis were observed in 4.5% (4) of cases. The potential biological behaviour of GIST is difficult to predict. The Consesus Guidelines on GIST prognosis, supported by the National Institute of health, suggest that mitotic index, size and tumor location can be considered as the most effective prognostic factors (3,8,13). These findings allowed Fletcher to combine these criteria in a new scale "risk of aggressive behaviour classification of GIST", considering only tumor size and mitotic count [26,27]. Our 88 patients were classified according to Fletcher risk classes as follows: 7 (7.95%) of patients were classified as

very-low risk group, 30 (34.09%) low risk, 15 (17.04%) intermediate risk and 36 (40.90%) high-risk. Miettinen criteria for the risk classification take into account mitotic count, size and tumor location [28,29]. Our 88 patients were classified according to Miettinen risk classes as follows: no risk 13 patients (14.70%), low 47 (53.40%), intermediate 18 (20.45%), high 10 (11.36%).

Surgical management entailed different technical options: 33 (37.5%) wedge resection (21 of which were located in the stomach, 7 in the ileum, 2 in the duodenum, 1 in the liver, 1 in the pancreas, and 1 in the esophagus); 41 (46.59%) partial organ resections (22 gastric resection, 13 resections of the small bowel, 3 colon resection, 1 colorectal resection, 1 duodenum resection, 1 esophagogastric resection); 8 (9.09%) total gastrectomy and 1 (1.14%) splenectomy; 5 (5.68%) resection "en bloc" (gastrectomy+right liver resection, gastrectomy+left liver resection, 1 gastric and ileum resection, 1 gastrectomy and splenectomy, 1 gastric and trasvers colon resection) (Table 1 and Figure 1). Of these latter, 4 had tumor rupture and peritonitis. The organs most targeted by metastasis were the liver (61.53%), ileum (15.38%), omentum/peritoneum (15.38%), while lymph nodes and extra-abdominal sites were rarely affected. Only one patient who underwent "en-bloc" gastric and transverse colon resection didn't experience tumor rupture and peritonitis. The first patient, who initially underwent total gastrectomy and left liver lobectomy, had 4 further interventions for disease relapse. He was 39 years old at the time of diagnosis. After the first surgery, the treatment with Imatinib was initiated at a starting dose of 400 mg, subsequently increased to 800mg after 12 months of therapy. At the end of the fifth year, during which 4 additional surgical attempts were tried, a complementary dose of 37.5 mg of Sunitinib was added to the chemotherapeutic scheme. He died after five surgical operations and 86 months of follow-up and partial response to Imatinib and Sunitinib. In our series we have not found any other patient who needed treatment with sunitinib as second-line.

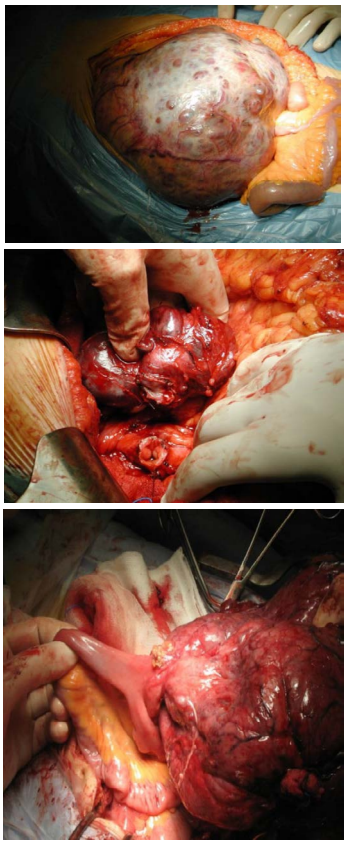

Figure 1: Pictures of stomach GIST (a), duodenum (b) and ileum (c).

In the second Table we classified our patients according to their clinical - pathological characteristics in 4 groups: Male >45 years and <45 years old, Female >45 years and <45 years old (Table 2).

Based on the clinical data, we found out that the group of male >55 years had the worst prognosis followed by female >55 years. They had the largest number of patients 28 (31.8%), with more cases of gastrointestinal bleeding 9 (10.22%), whose tumors are located mainly in the stomach 18 (20.45%) and ileum 6 (6.81%) but also in some cases the duodenum 1 (1.13%) and esophagus 1 (1.13%), which dimensions are greater 8 (9.09%) >5 cm <10 cm and 5 (5.85%) >10 cm, with high mitotic index 11 (12.5%) 6-10/50 HPF and 7 (7.95%) >10/50 HPF. This group has the highest number of cases with mutation of exon CD117, 14 (15.9%) and CD34, 5 (5.86%). The prevalent cell morphological type was as follow: spindle cell 16 (18.18%), epithelioid 7 (7.95%), mixed 5 (5.68%). They had the highest grade of malignancy: moderate 9 (10.22%), high 5 (5.68%) and the greater number of recurrencies: 6 liver (46.15%), 1 omentum (7.69%) and 1 spleen (7.69%) after 6 months of surgical resection and Imatinib Mesylate therapy into a total of 13 patients with recurrencies of 47 patients Imatinib Mesylate treated (Tables 2 and 3).

Patients (total 88 patients)	Male		Female	
	>55 years (28/88) (31.8%)	< 55 years (17/88) (19.3%)	> 55 years (25/88) (28.4%)	< 55 years (18/88) (20.4%)
GI bleeding vs No GI bleeding	9 (10.22%)	4 (4.54%)	6 (6.81%)	2 (2.2%)
	19 (21.59%)	13 (14.77%)	19 (21.59%)	16 (18.18%)
Tumor location				
Stomach	18 (20.45%)	11 (12.5%)	15 (13.63%)	12 (13.63%)
Ileum	6 (6.81%)	5 (5.68%)	5 (5.68%)	4 (4.54%)
Colon	2 (2.27%)	1 (1.13%)	-	-
Duodenum	1 (1.13%)	-	2 (2.27%)	-
Esophagus	1 (1.13%)	-	1 (1.13%)	-
Others*	-	-	2 (2.27%)	2 (2.27%)
Tumor size (cm)				
< 2 cm	3 (3.40%)	6 (6.81%)	5 (5.68%)	6 (6.81%)
> 2 cm < 5 cm	12 (13.63%)	6 (6.81%)	10 (11.36%)	6 (6.81%)
> 5 cm < 10 cm	8 (9.09%)	4 (4.54%)	6 (6.81%)	4 (4.54%)
> 10 cm	5 (5.68%)	1 (1.13%)	4 (4.54%)	2 (2.27%)
Mitotic count				
< 5/50 HPF	10 (11.36%)	12 (13.63%)	12 (13.63%)	13 (14.77%)
6-10/50 HPF	11 (12.50%)	5 (5.68%)	10 (11.36%)	5 (5.68%)
>10/50 HPF	7 (7.95%)	-	3 (3.40%)	-
Mutation status				
KIT exon CD117	14 (15.90%)	4 (4.54%)	9 (10.22%)	4 (4.54%)
KIT exon CD34	5 (5.68%)	-	1 (1.13%)	-
Wild-type	9 (10.22%)	13 (14.77%)	15 (17.04%)	14 (15.90%)
Morphological Type				
Spindle cell	16 (18.18%)	9 (10.22%)	15 (13.63%)	8 (9.09%)
		5 (5.68%)	6 (6.81%)	5 (5.68%)
Epithelioid cell	7 (7.95%)	3 (3.40%)	4 (4.54%)	5 (5.68%)

Mixed cell	5 (5.68%)			
Grade of malignancy				
Low	14 (15.90%)	16 (18.18%)	15 (17.04%)	15 (17.04%)
Moderate	9 (10.22%)	1 (1.13%)	7 (7.95%)	3 (3.40%)
High	5 (5.68%)	-	3 (3.40%)	
Number of recurrencies after 6 months of SR and IM therapy (total = 13 of 47 patients IM treated)				
Liver	6 (46.15%)	-	1 (7.69%)	1 (7.69%)
Ileum		-	2 (15.38%)	-
Omentum	-	1 (7.69%)	-	-
Spleen	1 (7.69%)	-	-	-
	1 (7.69%)			
Postoperative IM treatment (total = 47 patients)	18 (38.29%)	9 (19.14%)	15 (31.91%)	5 (10.63%)
Overall survival (3 years %)	45%	82%	52%	92%
	(Follow-up 1-126 months)		(Follow-up 1-96 months)	
Disease free survival (3 years %)	22%	76%	34%	86%
	(Follow-up 1-136 months)		(Follow-up 1-112 months)	
GISTs: Gastrointestinal Stromal Tumors; GI: Gastrointestinal; HPF: High Power Fields; IM: Imatinib Mesylate. *Others including omentum. mesentery of small intestine and large intestine. retroperitoneal. pancreatic. rectal. liver and spleen. SR: Surgical Resection.				

Table 2: Clinicopathologic characteristics of patients with primary GISTs among 4 groups (n=88).

Patients (total 47)	Nr. Patients (%)	Follow-up (months)	3-year DFS (Disease-free survival) (%)	Fletcher's criteria			
				VLR	LR	IR	HR
Alive (- DFR. - IM)	26 (55.31%)	Between 1 and 78 months	94%	8	16	2	
Alive (+DFR. + IM)	9 (19.14%)	Between 1 and 129 months	52%			4	5
Died from other diseases(-DRF.+/- IM)	8 (17.02%)	Between 1 and 61 months	76%	2	3	3	
Died from GIST (+DFR.+IM).	4 (8.51%)	Between 1 and 176 months	22%	4			
GISTs: Gastrointestinal Stromal Tumors; DFS: Disease – Free Survival; DFR: Disease – Free Recurrencies. IM: Imatinib Mesylate. -/+ DFR: non/presence of Disease – free recurrencies. -/+ IM: non treated/treated with Imatinib Mesylate;postoperative therapy; VLR: Very Low Risk; LR: Low Risk; IR: Intermediate Risk. HR: High Risk.							

Table 3: Patients treated with IM therapy in the follow-up.

They had the highest number of patients treated with postoperatively Imatinib therapy 18 (38.29%) and the worst 3-year overall survival of 45% with 3-year disease-free survival of 22%. Women group >55 years had a course similar to the group described above but with slightly better prognosis. Male group <55 years, 17 (19.3%) and Female <55 years, 18 (20.4%) had less patients and better final prognosis. They had fewer patients treated with Imatinib 9 (19.14%) and 5 (10.63%), better 3-year overall survival of 82% and 92%, 3-year disease-free survival of 76% and 86%. Fourty six (52.27%) out of 88 patients underwent postoperative treatment with Imatinib, 1 patient (1.13%) received a combination of Imatinib and Sunitinib. Twenty-three patients (26.14%) didn't need any further treatment besides surgery and a close follow-up through CT-scan and blood tests every 3/6 months. Eighteen patients (20.45%) were not contactable, discontinued the follow-up in our center.

We classified the 47 Imatinib treated patients into four groups (Table 3):

1) Patients alive, disease - free recurrencies, no need of further Imatinib treatment;

2) Patients alive, showing disease recurriences, still being treated with Imatinib;

3) Patients being treated not for GIST and died from other diseases;

4) Patients being treated for GIST and died from GIST.

We had a total of 13 patients with relapse of 47 patients treated with Imatinib Mesylate therapy in the post-operatively follow-up (6 months after first surgery and Imatinib therapy), these patients underwent a second surgery. Still 9 patients are in treatment with Imatinib and 4 died for GIST after Imatinib treatment and second surgery (Tables 2 and 3).

Twenty-six (55.31%) patients out of 47 had either a very-low, low or intermediate-risk tumors. They showed a good outcome following surgery with a 3-year disease-free survival of 94%, for this reason they discontinued Imatinib therapy after a follow-up period of 3 years. Nine (19.14%) patients with intermediate/high risk tumors had recurrences after resection and presented a 3-year disease-free survival of 52%, they are alive and still under treatment with Imatinib. Four (8.51%) patients with high risk tumors had 3-years disease-free survival of 22%, they relapsed after surgery despite Imatinib therapy and at the end died from advanced-GIST. Eight (17.02%) patients with very-low, low, intermediate and high risk tumors, with 3-year disease-free survival of 76%, operated and treated with Imatinib for GIST died from other diseases.

Conclusion

GISTs constitute an interesting chapter of oncological pathologies, because of their relative rarity, biological aggressiveness and diagnostic/therapeutic problems that frequently arise. The two main concerns regarding this class of tumors are: the exploitation of immunohistochemical tools such as the use of KIT (CD117) markers for diagnostic purposes, and secondly the development of monoclonal therapeutic options targeting CD117 in order to provide a new valuable tool against metastatic and recurrent GISTs [30-37].

We recommend that all patients with a GIST should be carefully and regularly followed-up for an indefinite period. Still nowadays surgery remains the unconditioned choice for very-low and low risk GISTs but in cases of intermediate, high-risk tumors, advanced or relapsed disease, new optimistic strategies are now represented by targeted therapies against c-kit. The clinical impact of the c-kit receptor targeting drugs (Imatinib-Gleevec) in GISTs has been so far confirmed in phase I and II trials [38-40], and it will likely improve the outcome of CD117-positive GISTs and of those cases not suited for radical surgery. In our study, we have seen that almost all patients treated with Imatinib after surgery had a good clinical response, only few patients with very advanced-GIST tumors at diagnosis had a partial response to the treatment and the results of secondary surgery were anyway generally poor. In summary, Gleevec is the only effective treatment for unresectable and/or metastatic GISTs affecting the pathogenesis of the disease. In addition, Gleevec has demonstrated to increase the survival of patients with metastatic and/or unresectable GISTs, in comparison with past therapeutic options [40-44].

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