Gastrointestinal Stromal Tumors: a single Center retrospective 15 years study

Ann. Ital. Chir., 2016 87: 426-432
pii: S0003469X16025574

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BACKGROUND: *Gastro Intestinal Stromal Tumors (GISTs) are defined as mesenchymal tumours that develop within the wall of the gastrointestinal tract. Surgery is the treatment of choice and may be indicated for locally advanced or previously non resectable disease after a favorable response to preoperative therapy with tyrosine kinase inhibitors.*
METHODS: *A retrospective analysis was conducted for all patients with a confirmed or suspected diagnosis of GIST who were admitted to the University Hospital of Parma from January 2000 to January 2015.The following parameters were reviewed and analyzed: age, sex, blood type, symptoms on presentation, tumor site, tumor size, mitotic rate, risk grade, histopathology and immunohistochemistry assays, type of cells.*
RESULTS: *All patients underwent elective surgery. Between January 2000 and January 2015, 61 patients were admitted to the OU General Surgery and Organ Transplantation, University Hospital of Parma and received surgical treatment for GISTs. Thirty-five were male (57.4%) and 26 female (42.6%). The mean age at diagnosis was 69.03 ± 10.07 years (range 29 – 89 years); males 69.6 ± 9.3 years (range 49 – 89 years) and females 68 ± 12.4 years (range 29 – 86 years). Larger tumor size, higher mitotic rate, higher risk rate, margin status contributed to poorer outcome (lower OS and DFS) as independent factors.*
CONCLUSIONS: *Radical surgery is the treatment of choice for resectable GISTs. Very low and low-risk tumor can be treated with surgery alone.*

KEY WORDS: Gastrointestinal Stromal Tumor, Margin Status, Overall Survival, Tumor size

Introduction

Gastro Intestinal Stromal Tumors (GISTs) are defined as mesenchymal tumours that develop within the wall of the gastrointestinal tract; in particular, GISTs originate from the interstitial cells of Cajal. Before the identification of the cells of Cajal, GISTs were generally considered as soft tissue sarcomas; this delay in the correct definition of GISTs is likely responsible for their underestimated incidence [1-3].

The oncogenic event that leads to GIST development is a gain of function gene mutation in one of the receptor protein tyrosine kinases KIT (also called CD117) or PDGFRA [1-3]. Surgery, laparoscopic or laparotomy approach, is the treatment of choice for patients with localized and potentially resectable lesions and may be indicated for locally advanced or previously not resectable disease after a favourable response to preoperative therapy [4].

This study reviews clinical, histopathological and immune - histochemical features, surgical treatment and diagnostic work-up of 61 cases of GISTs treated at OU

Pervenuto in Redazione Marzo 2016. Accettato per la pubblicazione Maggio 2016
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General Surgery and Organ Transplantation of Parma in the last fifteen-years to evaluate prognostic factors of this disease.

Materials and Methods

A retrospective analysis was conducted for all patients with a confirmed or suspected diagnosis of GIST who were admitted to our OU from January 2000 to January 2015. Only patients who underwent surgery were included in the study. The following parameters were reviewed and analyzed: age, sex, blood type, symptoms on presentation, tumor site, tumor size, mitotic rate, risk grade (according to Miettinen classification), histopathology and immunohistochemistry assays (CD117, CD34, S-100, SMA, caldesmon, desmin, cytokeratin and DOG1 expression), type of cells (spindle, epithelioid and mixed) and margin resection status (involved or free). Patients were staged pre-operatively through GI endoscopy (with or without biopsy), GI endoscopy ultrasound (with or without FNAB), CT or RMT scans. These surgical procedures were performed: minimally invasive surgical approaches (laparoscopic wedge resection, laparoscopic and endoscopic cooperative surgery) and open surgery (total or subtotal gastrectomy, segmental resection of small bowel, hemicolectomy, duodenocefalopancreasectomy, esophagectomy, excision of tumor mass). Details of neo-adjuvant and adjuvant therapy with tyrosine kinases inhibitors (TKI) were also considered in the study. Survival outcome in terms of overall survival (OS) and disease free survival (DFS) were calculated. Survival status was collected through the Parma's Register of Tumors and some data were recorded by contacting the patients directly; follow up was closed in January 2015.
Patients with missing data were excluded. The Chi-square test and Fisher's exact test were used to analyze qualitative parameters; and t tests were performed to compare different risk factors. OS curves and DFS curves were estimated using the Kaplan and Meier method. $P < 0.05$ was considered statistically significant. Statistical analysis was performed using the Statistical Product and Service Solution, SPSS version 21.0 (SPSS, Inc., Chicago, IL, USA)

Results

Between January 2000 and January 2015, 61 patients received at our operative unit surgical treatment for GISTs. The patients' characteristics about sex, age, blood group, tumor site and size are shown in Table I.
The primary symptoms on presentation depended on tumor location and size. Twenty-six patients (42,6%), complained of different symptoms, the most frequent of which were abdominal pain (15 cases) and GI bleeding (9 cases with melena and 1 case with hematemesis); only 1 patient presented with intestinal obstruction. Table II reports the clinical presentation of GISTs according to tumor size and tumor site.
In 13 patients, removal of the GIST was performed during surgery for other malignancy. In several of these cases, diagnosis was done during pre-surgical work up, while in others it was an incidental finding during surgery. Review of the oncological case history of all patients, 30 (49.2%) had no previous history of cancer, whereas 31

TABLE I - *Clinical and pathological characteristics of the population analyzed.*

Sex	**N**	**%**	**Tumor site**	**N**	**%**
males	35	57,4	esophagus	1	1.6
females	26	42,6	stomach	40	65.5
Age	mean (sd)	Range	duodenum	4	6.6
total	69,03 (± 10.07)	29 – 89	small intestine	10	16.4
males	69,6 (± 9.3)	49 – 89	colon	1	1.6
females	68 (± 12.4)	29 – 86	rectum	3	4.9
Blood group	n	%	omentum	1	1.6
A +	28	45,9	mesentery	1	1.6
A -	2	3,3	**Tumor size**	n	%
AB +	2	3,3	≤ 2 cm	16	26.2
AB -	2	3,3	> 2 and ≤ 5 cm	15	24.6
B +	3	4,9	> 5 and ≤ 10 cm	25	41
B -	1	1,6	> 10 cm	5	8.2
0 +	11	18	**Tumor risk**	n	%
0 -	3	4,9	very low	20	26.2
Clinical presentation	n	%	low	16	14.8
asymptomatic	35	57,4	intermediate	9	26.2
symptomatic	26	42,6	high	16	32.8

TABLE II - *Clinical presentation of GISTs according to tumor site ad tumor size.*

Clinical presentation	**Asymptomatic**		**Symptomatic**	
incidental finding during imaging procedures	23	(37,7%)	–	
incidental finding during surgery procedures	12	(19,7%)	–	
abdominal pain	–		15	(24,6%)
GI bleeding	–		10	(16,4%)
GI obstruction	–		1	(1,6%)
Clinical presentation according to tumor site	**Asymptomatic**		**Symptomatic**	
esophagus	1	(1,6%)	–	
stomach	24	(39,3%)	16	(26,2%)
duodenum	2	(3,3%)	2	(3,3%)
small intestine	6	(9,8%)	4	(6,6%)
colon	-		1	(1,6%)
rectum	1	(1,6%)	2	(3,3%)
omentum	1	(1,6%)	–	
mesentery	1	(1,6%)	–	
Clinical presentation according to tumor size	**Asymptomatic**		**Symptomatic**	
< 2 cm	14		2	
≥ 2 cm	20	25		

(50.8%) had a previous or concomitant diagnosis of oncologic disease, consisting in 6 cases in gastric cancer and in 5 cases in colorectal cancer. Histopathological examination was carried out in all patients. Microscopically, GIST cell morphology was spindle in 61 (75.4%), epithelioid in 7 (11.5%) and mixed in 8 (13.1%) cases. CD117 was positive in 55 (90.2%) and CD34 in 41 (67.2%) lesions. SMA and S-100 positivity occurred in 23 (37.7%) and 4 (6.6%) cases respectively. Caldesmon and desmin were tested only in a few patients. DOG1, a newly developed marker, was tested only in most recently examined specimens and was positive in all cases analysed (16 patients). Patients were classified as high, intermediate, low and very low risk (26.2%, 14.8%, 26.2%, 32.8% respectively) according to the Mienninen criteria. To estimate the value of mitotic rate and diameter of the tumor as independent factors in determining the risk grade, we calculated OS and DFS according to these two variables: using a t test for independent samples. Mitotic rate resulted to be a more useful prognostic factor for both OS and DSF, compared to tumor size ($p < 0,005$).

The most common diagnostic method used was abdominal CT scan in 47 patients (77%), followed by GI endoscopy (GIE) in 38 patients (62.3%), GI endoscopy ultrasound (GIEUS) in 15 patients (24.6%) and RMT scan in 12 patients (19.7%) (Table III). CT scan was able to detect lesions in 36 cases (size > 2 cm in 34 patients and ≤ 2 in 2 patients). RMT scan was suggestive of GIST in 9 patients (size > 2 cm in all cases). GIE revealed the lesion in 22 patients and in 20 of these, tumor size was > 2 cm; GIE was not diagnostic in 16 patients, 9 of which tumor size was ≤ 2 cm ($p= 0.003$). Likewise, GIEUS was positive in 13 patients, with 12 cases being > 2 cm; GIEUS was negative in 2 patients and in both cases lesion size was ≤ 2 cm ($p= 0.017$). Endoscopic examination identified the lesion in 22 cases and biopsy, applied in 19 patients, was positive in 6. FNAB during GI endoscopy ultrasound was applied only in 11 cases and was diagnostic in 7.

All patients underwent elective surgery; patients with acute presentation requiring emergency surgery were not considered in our paper. Laparoscopic resections were performed in 8 patients (13.1%) and conventional open surgical resection in 50 patients (82%). Conversion to laparotomy was necessary in 3 cases: the first patient had large exophytic gastric lesion (10 x 9 cm), not removable laparoscopically; the other two patients presented GIST as incidental finding during surgery for other disease that required open conversion.

From 2006, only 6 patients with high risk GISTs received adjuvant therapy with Imatinib Mesylate after radical resection and 1 patient with high risk and metastatic GIST received neo-adjuvant therapy before surgery. In these patients, c-kit and PDGFR mutations status was screened and mutations in c-kit exon 11 and PDGFRA exon 18 were identified in 6 and 1 patient respectively.

The median follow up period was 59.7 months (range: 2 – 167 months). During this period, 43 patients (70.5%) were alive and 18 (29.5%) patients died. Six patients died from GIST progression and 12 died for other causes. Recurrence or metastasis occurred in 9 patients (14.8%) whereas 52 patients were free from disease during follow up period. Overall survival and disease free survival rates for all patients were calculated using the Kaplan-Meier curves.

TABLE III - *Diagnostic work-up. GIE: gastro-intestinal endoscopy, GIEUS: gastro-intestinal endoscopic ultrasound, CT: computed tomography, MRT: magnetic resonance tomography, N: number, pt: patients .*

Diagnostic Work-up	N. pt	Diagnostic / Non Diagnostic (N. pt)	Tumor size ≤ 2 cm (N. pt)	Tumor size > 2 cm (N. pt)
GIE	38	22	2	20
	–	16	7	9
GIEUS	15	13	1	12
	–	2	2	0
CT	47	36	2	34
	–	11	11	0
MRT	12	9	0	9
	–	3	2	1

Univariate analysis revealed that larger tumor size, higher mitotic rate, higher risk rate, margin status contributed to poorer outcome (lower OS and DFS) as independent factors. OS according to risk grade was: 65% (very low risk); 87.5% (low risk); 88.9% (intermediate risk); 50% (high risk) respectively. DSF according to risk grade was: 100% (very low risk); 87.5% (low risk); 100% (intermediate risk); 56.3% (high risk) respectively. The analysis of OS and DFS calculated by Kaplan-Meier curves focused on two groups: very low, low and intermediate risk (group 1) and high risk (group 2) showing a considerable difference as reported in Fig. 1.
Furthermore, margin resection status was evaluated comparing surgical specimens with any (RO) or microscopic (R1) marginal involvement and OS and DFS calculated by Kaplan-Meier curves are reported in Fig. 2.
In the population analysed, 9 patients developed recurrence after surgery for primary disease; among them 7 did not receive adjuvant therapy with Imatinib Mesylate, 1 received it as neo-adjuvant therapy for metastatic disease at diagnosis and 1 was a non responder due to uncommon mutation. The treatment of these cases was surgical excision of tumor relapse for 2 patients and pharmacological therapy for the other patients.

Discussion

GISTs are the most common mesenchymal tumors of the gastrointestinal tract; epidemiological data indicate the overall incidence of GISTs to be 10-20 per million, with some reported differences in various countries [1-3] Men and women are affected at a similar frequency and only a few studies have shown a slight male predominance. In the studies presented by Miettinen et al. the median age of patients with GISTs at the diagnosis was 63 years and there was a light male predominance [3,16]; our paper shows a higher age at diagnosis (mean 69.03

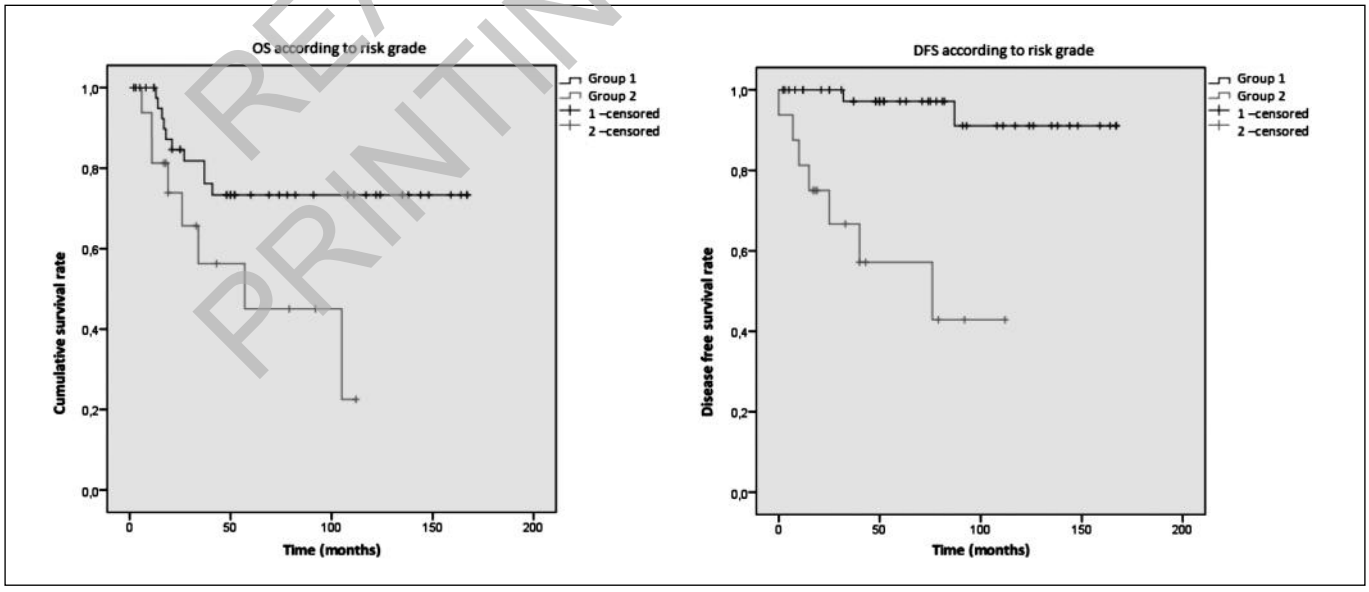

Fig. 1: (A) overall survival (OS) curves and (B) disease free survival (DFS) according to risk grade. Group1: very low, low and intermediate risk; group 2: high risk.

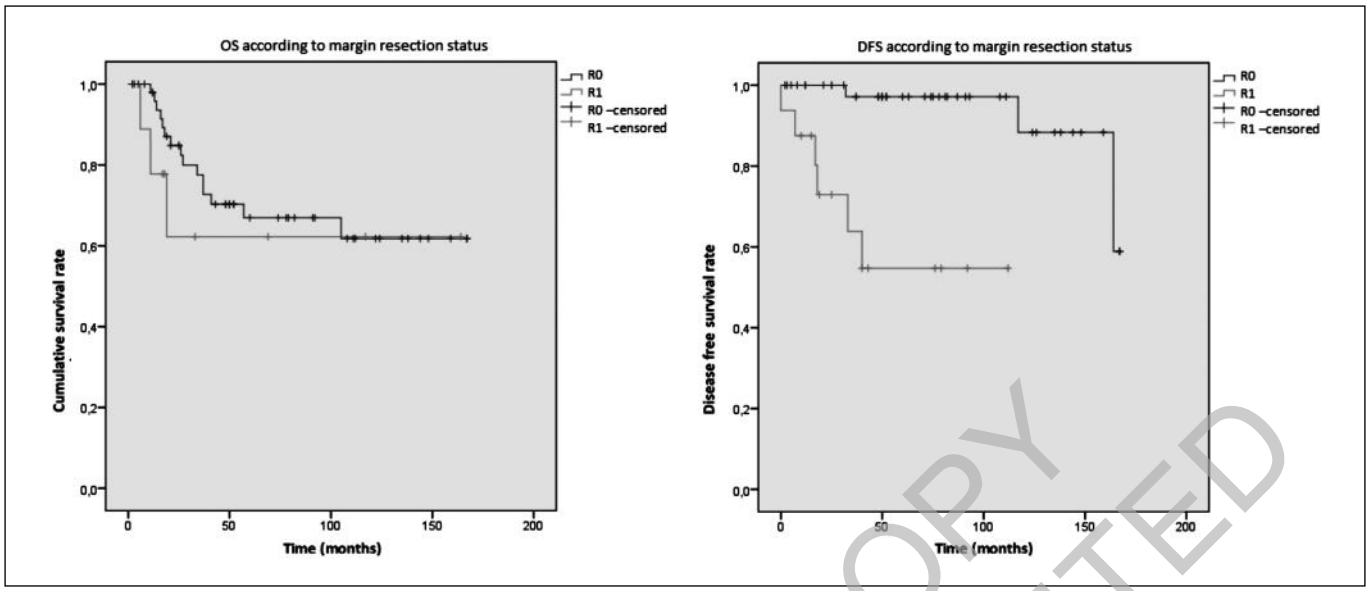

Fig. 2: (A) overall survival (OS) and (B) disease free survival (DFS) curves according to margin resection status.

years) with a men predominance of 57.4% vs 42.6% patients. No significate difference in age at diagnosis between the two sexes were found, consistent with literature data. Paediatric cases were not considered.

We examined the association between the ABO blood group – Rh factor and GIST and we did not observe any relationship between these factors, as reported by others [6]; indeed, the ABO trend reflects national distribution.

In the majority of cases symptoms can be absent or extremely vague unless the lesion is in a certain location or until the tumor growths to a certain size [7,8]. In our data 57,4% of patients were asymptomatic and diagnosis of GIST was incidental during surgery and imaging for other diseases. 42,6% were on the contrary symptomatic and the most frequent clinical presentation was abdominal pain or GI bleeding. We also found that tumor size was significantly related to clinical presentation ($p < 0.05$): in 92,3% of symptomatic patients tumor size was > 2 cm.

GISTs are more common in the stomach, jejunum and ileum and less frequent in the duodenum, rectum, colon and appendix, and oesophagus [1,3,5]. Similarly, in our study, the stomach was the most commonly involved site (65,6% of cases) followed by small bowel (16.5%), duodenum (6,6%) and rectum (4.9%).

Based on oncological case history, 50.8% of patients included in our database had a previous or concomitant diagnosis of oncologic disease; these gastrointestinal malignancies do not seem to be related to GISTs, considering the different origin. However, the presence of gastric or colorectal cancer allowed an early detection and excision of GISTs as incidental findings.

GISTs can be composed of spindle (70%), epithelioid (20%) or mixed (10%) cells and more than 95% of GISTs are positive for the tyrosine kinase receptor protein KIT. 60-70% of GISTs are positive for CD34, 30-40% are positive for smooth muscle actin, 5% are positive for S100 (usually focal), 5% are positive for desmin (usually focal), and 1% to 2% are positive for keratin (weak/focal) [9]. The antigen DOG1 (a calcium-dependent chloride channel) was recently introduced as a new marker to differentiate GISTs from other sarcomas [10]. His expression should be investigated together with other tissue markers at the moment of histological definition of lesion suspected for GIST as it is usually present, even in 5% of negative-KIT GISTs. In our work it was tested only in 16 patients and was positive in all cases analysed to confirm the high specificity and sensibility of this marker.

CT scan is the imaging modality of choice for initial evaluation, staging and follow-up of treatment response. MR scan is an alternative option indicated for rectal GISTs, for liver metastases and for cases in which CT scan is contraindicated [5,12,13]. GIE allows to identify GISTs as lesions which protrude from the deeper wall layers bulging into the organ lumen; with GIE and GIEUS samples of the tumor mass can be obtained with biopsy forceps or with FNAB.

We applied abdominal CT scan in 47 patients (77%), GIE in 38 patients (62.3%) and GIEUS in 15 patients (24,6%). As known in literature, biopsy could be associated with risk of tumor bleeding and dissemination, but the 2015 NCCN guidelines and 2015 AIOM guidelines state that biopsy is necessary to confirm the diagnosis of primary GIST prior to initiation of an eventu-

al preoperative neoadiuvant therapy [14,15]. Sepe et al. showed that FNAB frequently reveals spindle cells or is positive for specific GIST markers and has sensitivity as high as 80% [13]. In our series, preoperative biopsy or FNAB were applied in 19 and 11 patients respectively. Preoperative histologic diagnosis of GIST was confirmed in 13 cases: GIE with biopsy in 6 patients and GIEUS with FNAB in 7 cases. Considering the guidelines indications, we can say that preoperative histological diagnosis is not necessary for small reselectable neoplasms, as it can cause rupture of the tumor capsule with bleeding or risk of cancer spreading [13], but is absolutely useful for non resectable GIST that need preoperative neoadiuvant therapy.

It is important to distinguish localized disease, where complete (R0) negative margin is the main aim of surgical treatment, and unresectable or metastatic disease, where preoperative therapy could help down-staging the tumor in order to perform a less demolitive surgical intervention [1,3,5,14,15]. According to tumor size and location, different surgical approach may be proposed: the excision of a nodular lesion when small GISTs are incidentally found during other procedures at a very early growth stage; wedge resection for small to medium sized gastric GISTs when sufficient margins can be obtained; distal or total gastrectomies for larger gastric GISTs; segmental resection for intestinal GISTs [15]. When GISTs are densely adherent to adjacent organs, en bloc resection should be performed [3,5].

The choice to proceed with laparoscopic or open surgery should be based on the surgeon's experience and the possibility to reach and handle tumor localized in inconvenient sites. No absolute indication for laparoscopic surgery for GISTs has yet been established [4,14]. In our study laparoscopic wedge resection were performed in 8 patients (13,1%); the median tumor size of the patients who underwent laparoscopic resection was 3.5 cm (range 0.6-5 cm) which was smaller than that of open surgery, 6.26 cm (range 0.5-40 cm). Considering the risk grade indicated by pathologists at the moment of specimen observation, group distribution was significantly different comparing patients who underwent open and laparoscopic surgery: all patients treated with laparoscopic resections were low or very low risk. This to avoid the mentioned complications related to handling soft and fragile tumors whose capsule rupture increases with the size of the tumor itself.

In our study there was only 1 recurrence in patients who underwent laparoscopic resection and this patient presented hemoperitoneum at surgery.

The behaviour of GISTs is defined of mitotic rate of cell composing the lesion. In 2002 Fletcher et al. declared that tumor size and mitotic index were the foundation to risk stratification of GISTs. In general, tumor < 5 cm (and particularly those < 2 cm) have a lower risk of metastasis, whereas tumors > 5 cm (and particularly those > 10 cm) have a higher risk [3,14] Similarly, a mitotic rate < 5 mitoses per 50 HPF predicts a lower risk of metastasis, whereas a mitotic rate > 5 mitoses per 50 HPF indicates a higher risk of metastatic disease [3,5]. In 2006, Miettinen and Lasota [16] improved this risk scheme with the inclusion of a further parameter represented by the tumor anatomic location; they observed that gastric tumors have a more favourable prognosis than the intestinal ones with similar parameters and the risk scheme classification previously proposed was therefore adapted and endorsed by the National Comprehensive Cancer Network (NCCN) in 2010 [14].

To evaluate the prognosis in patients included in our database, we focused on two groups: very low, low and intermediate risk (group 1) and high risk (group 2); the analysis of OS and DFS showed a considerable difference between two groups ($p < 0,005$). Our study confirmed that tumor size, higher mitotic rate, higher risk rate and margin status are independent prognostic factors of both OS and DFS; in patient with the same risk grade, higher mitotic rate results to be the worse prognostic factor ($p < 0,005$) compared with tumor size. Long-term monitoring has showed that surgery alone is usually insufficient to control high-risk diseases. Introduction of IM improved the outcome of GISTs [6,17,18].

In case of locally advanced disease, metastatic disease and recurrent disease, target therapy with Imatinib Mesylate (IM - Glivec, *Novartis*) is the treatment of choice. In 2002 Dagher R. [17] demonstrated its efficacy in a patient with multiple metastatic GIST who had no clinical response after chemotherapy and in the same year IM was approved by the Food and Drug Administration (FDA) for the treatment of malignant metastatic and/or unresectable GISTs [17]. Patients which still are not responsive are treated with a second-line tyrosine kinase inhibitor, Sunitinib malate (Sutent, *Pfizer*). The only proven third-line treatment for Imatinib- and Sunitinib-resistant GISTs is now represented by Regorafenib (Stivarga, *Bayer*) [14,15]. New single drugs such as Nilotinib and Sorafenib are under investigation for patients who find that Gleevec or Sutent are no longer effective in battling GISTs and also combined or integrated therapies could be discussed in selected patients [14.15].

In our study only six patients underwent therapy with tyrosine kinases inhibitors: they were high risk GISTs included in the follow up oncological programs after surgery. No patients before 2006 underwent therapy with IM. The limitation of this study about the role of therapy with IM is the low number of patients treated: in the cohort analyzed a lot of patients with advanced disease didn't undergo IM therapy; most of cases were before 2006.

Conclusion

Biopsy is necessary to confirm the diagnosis of primary GIST prior to the initiation of preoperative therapy. Radical surgery is the treatment of choice for resectable GISTs. Very low and low-risk tumor can be treated with surgery alone. A laparoscopic approach may be consid-

ered for select GISTs in favourable anatomic locations by surgeons with appropriate laparoscopic experience. Tumor size, higher mitotic rate, higher risk rate and margin status are independent prognostic factors of both OS and DFS; mitotic rate results to be the worse prognostic factor if compared with tumor size. Follow up recommendations should be based upon experts integrated opinions and histopathological evaluation of the lesion, distinguishing patients with localized disease who may not need a strict follow up and patients with unresectable, metastatic or recurrent disease who require tyrosine kinase inhibitor administration with adequate surveillance in terms of response or resistance to therapy.

Riassunto

PREMESSA: Tumori Stromali Gastrointestinali (GIST) sono definiti come tumori di origine mesenchimale mesenchimale che si sviluppano all'interno della parete del tratto gastrointestinale. La chirurgia è il trattamento di scelta e può essere indicata per patologia localmente avanzata o giudicata non resecabile prima di un ariposta positiva al trattamento con inibitori della tyrosine kinase.
METODI: Abbiamo condotto una analisi retrospettiva su tutti i pazienti con diagnosi sospetta o confermata di GIST che sono stati ricoverati presso l'ospedale universitario di Parma dal gennaio 2000 al gennaio 2015. Abbiamo analizzato i seguenti parametri: sesso, età, gruppo sanguigno, sintomatologia, dimensioni del tumore, sede del tumore, indice mitotico, grading, risuslttao istologico e immunoistochimico, tipo di cellularità.
RISULTATI: Tutti i pazienti sono stati sottoposti a chirurgia in elezione. Tra genaio 2000 e gennaio 2015, 61 pazienti sono stati ricoverati presso il reparto di Chirurgia generale e Trapianti d'Organo, dell'Azienda Ospedaliera Universitaria di Parma con trattamento chirurgico. 35 erano di sesso maschile (57,4%) e 26 di sesso femminile (42,6%). L'età media alla diagnosi era di 69.03+/-10.07 anni (range 29-89 anni); maschi 69.6+/-9.3 anni(range 49-89 anni) e femmine 68+/-12.4 anni (range 29-86 anni)
I tumori che presentavano come fattori indipendenti un diametro maggiore, un più alto indice mitotico, un rischio più alto, l'interessamento dei margini di resezione presentavano un outcome peggiore (più basso OS e DFS).
CONCLUSIONI: La chirurgia radicale è il miglior trattamento per i GIST resecabili. I tumori a basso rischio possono essere trattati con la sola chirurgia.

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