Twelve years of gastric GIST

A retrospective study of laparoscopic and open approach

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Twelve years of gastric GIST. A retrospective study of laparoscopic and open approach

PURPOSE: *The authors wanted to evaluate the outcome of laparoscopic and open resection for gastric GISTs, in the long and short run with a retrospective study based on 63 consecutive patients.*
METHODS: *Two surgical groups were compared according to age, sex, ASA group and Surgical procedure: a laparoscopic resection was performed on 30 patients (47,7%) while the open approach was preferred for 33 patients (52,3%). Duration of surgery, blood loss, positive resection margins, postoperative morbidity, postoperative ileus, hospital stay, tumor's mean dimensions, degree of malignancy and recurrences rate and 5-years mortality were compared in subgroups.*
RESULTS: *Significant differences between Open Gastrectomy group and Laparoscopic Gastrectomy group were found in blood loss 425 ml (180-610) vs 137 ml (110-320), postoperative ileus 4,1D (3-6) vs 2,3D (1-7), hospital stay 15D (8-25) vs 10D (8-17), neoplasia mean dimensions in patients who underwent total gastrectomy (7,1±0,9 cm vs 5,3±0,5 cm) and atypical gastrectomy (4,3±0,8 cm vs 2,2±0,3 cm), high degree of malignancy in patients who underwent subtotal gastrectomy (4 vs 0 pz) and 5-years mortality in patients who underwent total gastrectomy (36.6% vs 12.5%).*
CONCLUSIONS: *Poor blood loss, shorter postoperative ileus and shorter hospital stay in the LG group show that laparoscopy can be performed safely and efficiently in gastric GISTs.*

KEY WORDS: Cajal cell, Gastric neoplasia, GIST mortality, GIST, Laparoscopic gastrectomy

Introduction

Gastric GISTs (Gastrointestinal Stoma Tumors) are rare: they represent 0.2% of all gastrointestinal tumors [1]. They are also the most common mesenchymal tumors of the gastrointestinal tract. Inappropriately classified in the past as Leiomyomas, Leiomyoblastomas and Schwannomas, in the late 90's they were classified as a single neoplastic entity, when immunohistochemistry had identified the gene KIT (CD117) [2]. They derive from Cajal cells probably arising from cells of the smooth muscle of the viscera [3,4] Fletcher et al. [8] divided GISTs into malignancy classes based on the risk of metastatic disease: in this way they developed a macroscopic and histological classification for these tumours.
Gastric GISTs are suitable for a laparoscopic approach, because they rarely involve lymph nodes [9-11] and because they require only gross negative resection margins [12-15]. Tumor's location and dimensions are limitations for the laparoscopic approach, because there are not clear guidelines about them so far [16].
By the means of a 12-years retrospective study the authors wanted to evaluate the outcomes of laparoscopic and open resections for gastric GISTs, in the long and short run.

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Materials and Methods

This is a retrospective study based on 63 consecutive patients with suspected gastric GIST at San Salvatore Hospital of L'Aquila between November 2002 and December 2014.
This group of patients had been selected from a bigger one. At the beginning there were 78 patients but 15 of them were excluded from the study for clinical contraindications (ASA score ≥4) (5 patients), metastatic disease at an advanced stage (4 patients), infiltration of adjacent organs (4 patients) and high intestinal obstruction (2 patients) (Fig. 1).
We divided the patients in two groups on the basis of the laparoscopic and open approach (group LG and OG group) and we analyzed the type of surgery performed. Two surgical groups were compared according to age, sex, ASA group (Tab. I) and Surgical procedure (Fig. 1). Duration of surgery, blood loss and resection margins were compared during the preoperative time. Postoperative ileus, complications and length of hospital stay were compared in the postoperative time (Tab. II). According to different surgical procedures some subgroups were identified (Tab. III, IV). The distribution of GIST (both in groups and in subgroups) was evaluated by the stratification system of Fletcher et al. [8]. Tumour's dimensions and mitotic count were considered as predictor parameters for the degree of malignancy. Gastric GISTs were classified for malignant potential as follows: low risk (2-5 cm and <5 mitoses/50 HPFs), moderate risk (<5 cm and 6-10 mitoses/50 HPFs or 5-10 cm and <5 mitoses/50 HPFs), and high risk (>5 cm and >5 mitoses/50 hpfs). moreover, recurrence of tumor and mortality rate at 5 years was at least compared between the two groups (Fig. 2)

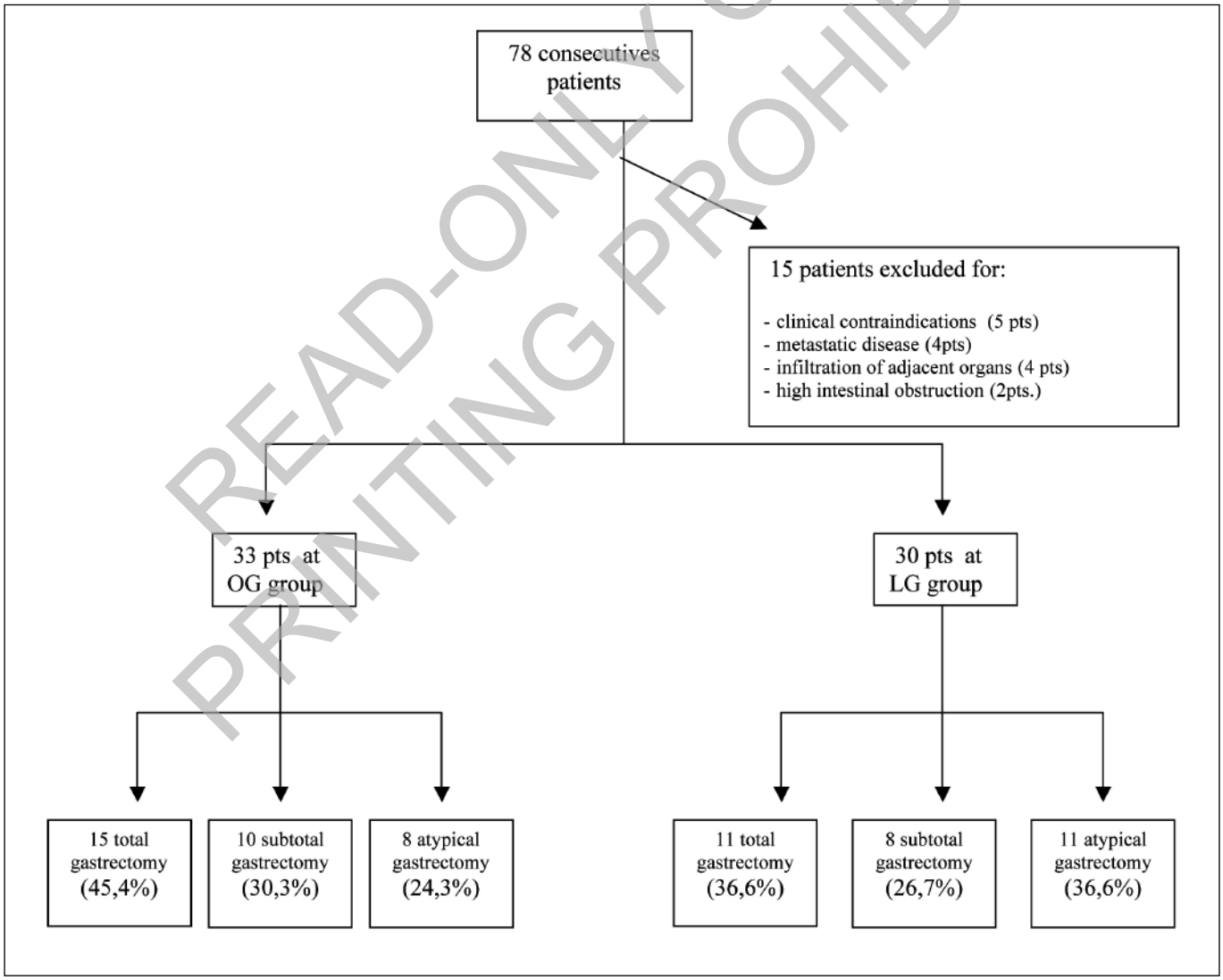

Fig 1: The various stages of trial, including exclusions.

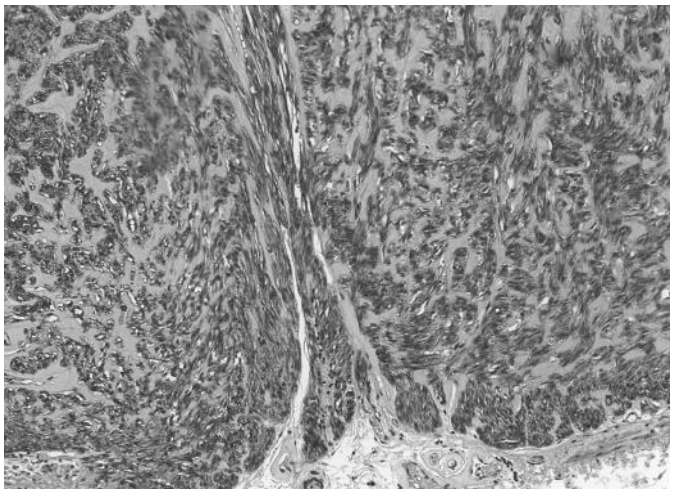

Fig 2: Immuno-histochemical features of GIST: c-KIT/ CD117 (tyrosine kinase growth factor receptor) positivity – 10X.

Statistical Analysis

The sample size of the study was calculated *a priori* on the assumption that it would have been clinically relevant to have a 15% reduction in the parameter (blood loss, duration of surgery, postoperative ileus between laparoscopy and laparotomy) with a 10% standard deviation. Furthermore, a power (1-β) of 80% was computed for the two-sided null hypothesis. A sample size of at least 15 patients was needed in each group to have a type error of less than 5% and a type II error of less than 20%, using a two-tailed test. Comparisons between groups were on an intention-to treat basis. The primary end points was to evaluate the response to laparoscopic and laparotomic treatment in terms of hospital stay, complications, local recurrences et mortality at five years to obtain useful data for the choice of the laparoscopic and laparotomic selection criteria. The secondary end points were to evaluate the characteristics of the tumor based on the gastric location. The normality distribution of the data was checked with the Shapiro-Wilk test. Data were analyzed using non-parametric statistics, which are more powerful when the data show a skewed distribution. Since the data were not normally distributed, an analysis of variance (non-parametric Friedman's repeated measures comparisons) was performed in both groups to determine differences between post-operative values and baseline. In the presence of significant difference, *post-hoc* analysis were made using the Mann-Whitney *U* test, to compare the values between the two groups Thus, all continuous variables were expressed as mean and standard deviation and compared using the Mann-Whitney *U* test. χ^2 test and Fisher's exact test were used to compare nominal data. Statistical calculations were performed with the help of Stata/MP 12.1, and a *P* value of less than 0.05 was considered to indicate statistical significance.

Results

A laparoscopic resection was performed on 30 patients (47,7%) while the open approach was preferred for 33 patients (52,3%). Laparoscopic approach was chosen on the base of the tumor size, lower than 5 cm (10 patients), the presence of adhesions due to previous laparothomies

Table I - *Surgical groups. Characteristics*

	n. pts	Age	Sex W/M	ASA II	ASA III
OG group	33	62.2 (45-76)	19/24	9	24
LG group	30	57.8(48-71)	18/22	19	11

Table II - *Surgical groups. Intervention results and complication*

	OG group	LG group	p value
Duration of surgery	228 min (150-360)	245 min (120-280)	ns
Blood loss	425 ml(180-610)	137 ml(110-320)	p< 0.05
Positive resection margins	0	0	ns
Postoperative morbidity	3 pts (11%)*	2 pts (8%)**	ns
Postoperative ileus	4,1 days (3-6)	2,3 days (1-7)	p< 0.05
Hospital stay	15 days (8-25)	10 days (8-17)	p< 0.05

* 3 postoperative pneumonia
** 2 abscesses treated with guided TC drainage

(9 patients) and the neoplasia' site (3 patients had a tumor involving the cardias) (Fig. 1).
The surgical approach was chosen during the operation.

Operative Tecnique

An "atypical resection" (characterized by partial dissection of the lesser and greater omentum lateral portion, gastro-phrenic ligament and short gastric vessels section and abdominal esophagus mobilization) was performed on neoplasm involving the large gastric curve. The gastroepiploic vascular arcade was divided as needed, using Harmonic Scalpel (Ultracision@ - Ethicon Endo-surgery Inc., Cincinnati. Ohio, USA). The large gastric curve removal was done by a 45 mm linear stapler GIA® (Ethicon Endo-surgery Inc., Cincinnati. Ohio, USA) upstream of the pylorus to the central portion of the gastric fundus. The surgeon tried to avoid a vagotomy, because it could have affected the postoperative gastric motility.
A "subtotal gastrectomy" with trans mesocolic Y-Roux reconstruction of digestive tract was performed on lesions situated in the distal 2/3 of the stomach, on the front or back wall of the stomach or in the small gastric curve.
A "total gastrectomy" with trans mesocolic Y-Roux reconstruction of digestive tract was performed on lesions involving the proximal third of the stomach.
In both cases the demolitive phase was performed by the means of ultrasonic dissector, while the reconstructive phase was carried out by the same linear stapler used for the atypical resection.
The integrity of stapler lines was controlled in all cases by the application of methylene blue via nasogastric tube.
A postoperative control of stapler lines was performed on all patients (5 days after resection, before resuming oral nutrition) by the means of CT-Scan after oral intake of contrast medium.
The laparoscopic approach had the same indications; it needed endoscopic assistance to evaluate the exact location of the tumor. The operative technique involved the placement of 4 laparoscopic trocars. The lymphadenectomy D2 was avoided, because it has no curative significance on these neoplasia. A follow up had been performed by endoscopy and abdominal CT-scan on patients of both groups every 6-12 months, in order to evaluate local recurrence and distant metastases.
Patients' mean age was 60 (range between 45 and 76) in both groups. There were 37 women and 46 men. ASA score is showed in Table1. There are more ASA III patients in the Open Gastrectomy (OG) group compared to Laparoscopic Gastrectomy (LG) group (24 vs. 11). No patient required neoadiuvant or biological therapy.
In the OG group 15 patients (45,4%) - including 3 gastro-esophageal junction GISTs - underwent total gastrectomy, 10 of them (30,3%) underwent subtotal gastrectomy and 8 patients (24.3%) underwent atypical gastrectomy.
In the LG group 11 patients (36.6%) underwent total gastrectomy, 8 patients (26.7%) underwent subtotal gastrectomy and 11 (36,6%) underwent atypical gastrectomy.
A Laparoscopic Gastrectomy was successfully performed on 28 of 30 patients (93.2%). In two patients the surgery was converted to Open Gastrectomy because of intraoperative splenic ruptures.
Table II shows surgery's mean duration: 228 minutes (range 150-360 min) for the OG group and 245 minutes (range 120-280 min) for the LG group (p=n.s.).
Blood loss was higher in the OG group than in the LG group: 425 ml (range 180-610 ml) versus 137 ml (110-320 ml) ($p<0.05$).
Resection margins had negative results in both groups.
No differences with regard to postoperative morbidity: 3 postoperative pneumonia (11%) in the OG group and 2 abscesses (treated with guided TC drainage) in the LG group (8%). These abscesses derived from small serous endoabdominal collections with bacterial superinfections. This prevalence of respiratory complications in the OG group may be due to a prolonged bed rest and to a bigger number of ASA III patients in the OG group.
No anastomotic leakage of linear suture in both groups.
Another significant difference was found in postoperative ileus: 4,1 days (range 3-6 days) in the LG group and 2,3 days (range 1-7 days) in the OG group ($p<0.05$).
Hospital stay was 15 days (8-25 days) in the OG group and 10 days (8-15 days) in the LG group ($p<0.05$).
The mean tumour size was 6,1 cm in the OG group

Table III - *Surgical groups. Intervention and median size*

Group	Median size	Median Size/Surgery Subgroup	
Open Gastrectomy	6.1 cm	7,1±0,9 cm	total gastrectomy
		5.1±0.7 cm	subtotal gastrectomy
		4,3±0.8 cm	atypical gastrectomy
Laparoscopic Gastrectomy	3.5 cm	5.3±0,5 cm *	total gastrectomy
		4.6±0.8 cm	subtotal gastrectomy
		2.2±0.3 cm*	atypical gastrectomy

*$p<0.05$

and 3,5 cm in the LG group. Tumour size distribution in subgroups is shown in Table III.

As regards the OG group, in 8 patients who underwent Total Gastrectomy and in 4 patients who underwent Subtotal Gastrectomy, the histological examination of surgical specimens showed high malignant potential GISTs. As concerns the LG group, the high malignant potential GIST was found in 6 patients who underwent Total Gastrectomy and in just one who underwent Atypical Gastrectomy (Table IV). The distribution of GISTs' degree of malignancy in the OG and LG group shows significant differences in Subtotal Gastrectomy just for the high grade of malignancy: 4 cases in the OG group and no one in the LG group ($p<0.05$) (Table IV).

As for the histology, 44 GISTs (69,8%) were of spindle cell type and 19 (30,2%) were of epithelioid type. The himmunohistochemistry was positive for KIT and for Vimentin in 60 cases (95,2%); 51 cases (81%) showed positivity for CD34; 6 cases (10%) had α-smooth muscle actin and 21 cases (33%) were positive for S-100. P53 protein was negative in all cases. PDGFRA was positive in 9 (14,2%) cases.

The lymph nodes invasion was neglected because it is poorly indicative of disease progression [12].

The adjuvant treatment was the biological therapy with Imatinib Mesylate and chemotherapy according to NCCN guidelines [17].

The mean follow up was of 42 months: 35 months in the LG group and 47 months in the OG group (p= n.s.). In the OG and in the LG group there were 8 and 3 recurrences respectively. As for the 8 patients of the OG group, 7 (21.2%) underwent Total Gastrectomy and one (3%) underwent Subtotal Gastrectomy. In this group recurrences were 2 peritoneal carcinomatosis and 6 liver metastases. As for the 3 patients of the LG group, 2 patients (6.6%) underwent Total Gastrectomy and one of them (3,3%) underwent Subtotal Gastrectomy. Their recurrences were liver metastases (Table V). In 9 of these patients (81,8%), recurrences developed in the first 28 months of follow up.

The rate of local recurrence was 1,6% in both groups. In fact, a patient with a moderate risk GIST treated with Laparoscopic Atypical Gastrectomy developed a local recurrence 54 months after gastric resection. On the other hand, a patient treated with Open Total Gastrectomy followed by Y-Roux reconstruction, had not recurrence after 120 months of follow up.

The average mortality at 5 years was 45,3% in the OG group and 19,1% in the LG group ($p< 0,05$). Table V shows patients' death rates according to 3 surgical techniques done in the 2 groups. A further significant difference is in the death rate of patients who underwent Total Gastrectomy in the OG group and in the LG group: 36,3% and 12,5% ($p< 0,05$) respectively.

Discussion

GIST is a rare cancer that originates from Cajal cells, interstitial pacemaker cells [1,3-7]: GIST shows positivity to tumor markers that can be found also in normal Cajal cells [1,3]. The immunohistochemical examination shows the over expression of KIT or CD34 gene in 90% of cases. Therefore, the positivity for the KIT gene is enough to make anatomopathological diagnosis of GIST [1-3,6,18] (Fig. 2). Other histological features are the negativity to S-100 and SMA (smooth muscle actin), over expressed in nerve cells and muscular cells respectively:

Table IV - *Surgical groups - Intervention and degree of malignancy*

	Total	gastrectomy	p	Subtotal	gastrectomy	p	Atypical	gastrectomy	p
	OG	LG		OG	LG		OG	LG	
High risk	8	6	ns	4	0	*	0	1	ns
Mod. risk	5	3	ns	4	5	ns	3	4	ns
Low risk	2	1	ns	2	3	ns	5	7	ns

* $p<0.05$

Table V - *Surgical groups. Intervention, recurrence and mortality*

	OG group Total Gastrectomy	OG group Subtotal Gastrectomy	OG group Atypical Gastrectomy	LG group Total Gastrectomy	LG group Subtotal Gastrectomy	LG group Atypical Gastrectomy
Recurrence	7 (21.2%)*	1 (3%)	0	2 (6.6%)*	1 (3.3%)	0
5-Year Mortality	12 (36.3%)*	3 (9%)	0	4 (12.5%)*	2 (6.6%)	0

* $p <0.05$

in this way it is possible to make differential diagnosis with gastric Schwannoma and Sarcoma. Genetic analysis of the PDGFRA is necessary to evaluate an eventual post-operative therapy with Imatinib Mesylate. Over expression of PGFRA is not associated with its mutation, it occurs up to 85% of cases, while the mutation occurs up to 5-7% [8,18,6,19].

Thanks to modern imaging techniques, it is often easy to plan the best approach to resect these gastric neoplasia; the surgical approach is based on tumor dimension and on its location: small tumors in distal gastric portions can be better treated with laparoscopy, while larger and more proximal tumors can benefit from open surgery. Laparoscopic gastrectomy shows obvious advantages: it is minimally invasive and it has the same short- and long-term efficacy compared with traditional open surgery in the treatment of gastric cancer [20-23]. No evidence in literature about guide-lines regarding the choice of open approach. Sasaki et al. suggested a tailored surgery for the choice of the surgical technique [16].

Poor blood loss, shorter postoperative ileus and shorter hospital stay in the LG group show that laparoscopy can be done safely and efficiently in gastric GISTs. Moreover, this has implications in hospital costs, pain management, and patient mobility [22]. The results of our study are similar to those found in literature, but with a minor complications rate [22,23].

Complications rates in LG and OG groups were similar: no significant difference in postoperative morbidity was observed between the two groups (8% vs. 11%; P=ns). The faster healing in patients who underwent laparoscopy reduces the incidence of postoperative pneumonia (Table II), remarking the safety of this approach. In the LG group there were two cases of intra-abdominal abscesses, treated with drug therapy. They were not due to an error in surgical technique, but they derived from patients' not optimal clinical conditions: they were diabetics and they had cardiopulmonary disease (ASA III). A recent meta-analysis found in literature shows that there is no significant difference in the rate of intra-abdominal fluid collection and abscess between LG and OG group (OR 0.34, 95% CI 0.05 to 2.17, P = 0.25) [24].

The presence of loco regional lymph node repetitions is estimated from 1.1% to 3.4% [6-8] for GIST. Thus, disease progression and patients' outcome depend on tumor size and on mitosis number, according to the stratification system of Fletcher et al. [8]. Anyway, our study demonstrates that dimension more than mitoses number influences the degree of malignancy. The comparison between Total-OG group and Total-LG group shows that a significant difference in 5-years death-rate (Table V) corresponds to a significative difference in tumors' dimensions (Table III), but not to malignancy (Table IV). Thus, a lower mitotic index does not guarantee a better outcome, as supported by Pidhorecky et al. [12] and Nowain et al. [13].

Because of the rarity of lymph nodes involvement, routine lymphoadenectomy is not currently recommended. For gastric GIST lymphoadenectomy standardization as for gastric adenocarcinomas does not exist [12]. In our study infact, a higher recurrence rate was found in patients who underwent a total gastrectomy, demonstrating that GIST progression depends on tumor's malignancy, not on lymph nodes excision. Data in Table V, as those find in literature [6,19,24-26], show that radical surgery does not improve survival in patients with high malignant potential neoplasia, compared to conservative surgery with wide resection margins. A total gastrectomy with wide resection margins, avoiding tumor's rupture, is the most commonly used surgical technique to treat gastric GISTs, because of the lack of clear guidelines [7,12,16].

An "en bloc" resection for GISTs involving contiguous organs is recommended. A partial resection is suitable just for palliative purposes (i.e. to solve organs' compression or occlusion). However, partial resection worsens the prognosis, as tumor's rupture can result in local recurrences involving peritoneum and the surrounding organs [6,7,12-15]. In our opinion, laparoscopic approach decreases the risk of tumor's breakage, and so local recurrences, because it reduces trauma and neoplasia's manipulations. In this regard, the lower local recurrences' rate in the LG group may be explained (Table V). Laparoscopy, in addition to the clear benefits of less invasiveness, may be therefore a factor that influences positively the prognosis of these tumors.

A well-defined follow-up protocol for GIST is not available. Some work show CT-Scan efficacy for the evaluation of tumor's response to the treatment with Imatinib Metylate [14]. Anyway, the exact role of CT-scan and its frequency in gastric GISTs' follow-up is not yet well-defined: it varies between 6 and 12 months, according to neoplasia's malignancy degree, as in our study.

About the 80% of tumour recurrences occurs within the first 24 months of follow-up [27], data confirmed also in our study (81.8%). The peak of recurrence in our study is the same in both groups. Even if there is a shorter follow-up in LG group, there is an accurate percentage of recurrences rate.

Recent data in literature show that patients with malignant gastric GISTs who undergo complete gastric resection, have a recurrence rate of about 50%, a median time of occurrence of 18-24 months and a 5-years survival of 50% [7,19].

Liver and peritoneum are the main organs involved in case of relapse [6,7,19,24]. Liver is involved in more than 60% of cases, representing the only repetition site in 44% of cases [19], while extra abdominal repetitions are found just in the advanced phases of the disease. Novitsky et al. [25] reported a 92% of 5-years disease-free survival for 4,4 cm tumors. Other authors reported similar results for gastric GISTs up to 5 cm [26]. DeMatteo et al. [19] highlighted that the responsivity to the biolog-

ical treatment with Imatinib determines a better survival, which is of 100% in the first 2 years, with a disease progression just in 61% of cases. The refractoriness to this biological treatment results in a 2-years survival of 36%, with a disease progression in 100% of cases. With the comparison of Tab 3 and 5, we find a 5-years mortality of 36.3%, 12.5%, 9% e 6,6%, respectively for GISTs of 7,1 cm, 5,3 cm, 5,1 cm e 4,6 cm. It's interesting that survival for Atypical Resection is the same (0%) between the two groups, despite the significant difference in tumors' mean dimensions in the two groups (Table III). This occurrence may indicate a different neoplastic progression for gastric GISTs according to their location. Anyway there are no data in literature that support this hypothesis. In this regard, further studies about large gastric curve Cajal cells could provide some useful data.

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