

Surgical treatment of gastric stromal tumors: laparoscopic versus open approach



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Surgical treatment of gastric stromal tumors: laparoscopic versus open approach

AIM: *Gastrointestinal stromal tumors (GIST) are quite rare tumors, but yet they are the most common mesenchymal lesions of gastrointestinal tract. Their outmost frequent origin site is stomach and presently surgical resection is the mainstay in the treatment of gastric non metastatic GIST. Their peculiar characteristic of growth and poor metastatic tendency make this tumors particularly prone to be managed by minimally invasive technique.*

Presenting our experience we want show the feasibility and safeness of laparoscopic approach for gastric GIST and its benefits versus traditional open surgery and pointing out short term and long terms outcomes.

PATIENTS AND METHODS: *In our series we included 60 patients who underwent surgery for gastric GIST from 2004 to 2014 at Clinica Chirurgica of Università Politecnica delle Marche. Patients were divided in two group according with surgical approach (open or laparoscopic). Criteria of exclusion were metastatic disease and palliative purpose of surgical resection. All patients underwent endoscopic ultrasonography, fine needle aspiration, TC/MRI or PET before surgery. However most of the definitive diagnosis were postoperative. CD117 and CD34 immunohistochemical positivity were considered suggestive for GIST. Tumors were classified in four different prognostic groups according with pathological findings (size and mitotic count) as reported in Fletcher classification. None of the patients received Imatinib before surgery. All patients underwent follow-up with Computerized Tomography (TC) and/or Magnetic Resonance (MRI) repeated every year (mean 51.98 ± 35.68 months).*

RESULTS: *We performed open surgery on 22 patients (36.7%) and laparoscopic wedge resection on 38 patients (63.33%); one of these underwent robotic wedge resection by da Vinci® surgical system.*

The median age at diagnosis was 64 years (range= 45-71).

Patients with gastric GIST presented with various symptoms, including fatigue secondary to anemia, intraluminal gastrointestinal bleeding, abdominal pain, abdominal mass, vomiting and syncope.

In 26 patients (43.3%) gastric GISTs were detected incidentally during abdominal exploration, endoscopy, or radiologic imaging. Tumor dimensional difference between the two groups was not significant (mean 4.75 cm, range= 2-13).

Operation time was significantly lower in laparoscopic approach (82.4 versus 117.8 min). We did not experience of intraoperative or post-operative complications in laparoscopic group. Conversely 4 patients of open group were transfused for anemia. In our series we didn't observe recurrence or metastasis at mean follow up period of (range= 49-120 months).

CONCLUSIONS: *Laparoscopic surgery is a minimally invasive approach to the treatment of GISTs and offers many advantages such as short hospital stay and low morbidity.*

In the meantime oncological outcomes of laparoscopy for gastric GIST, assessed as tumor free resection margins and recurrence rate, are comparable to traditional open strategy.

KEY WORDS: Gastrointestinal stromal tumors, Laparoscopy, Minimally invasive surgery, Stomach

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Introduction

Gastrointestinal stromal tumors (GIST) are quite rare tumors, representing 0.3-3% of all gastrointestinal tumors, but yet they are the most common mesenchy-

TABLE I - Patients characteristics

Variables	Patients (n=60)	LG (n=38)	OG (n=22)	p
Sex				1.000
Male	30/28 (50%)	16/38 (42.1%)	12/22 (54.5%)	
Female	30/28 (50%)	18/38 (47.4%)	10/22 (45.4%)	
Age				0.466
Mean (range)	61.53 (45-75)	60.88 (45-70)	64.36 (53-81)	
Median(1°- 3° percentile)	64 (56.25-68.5)	62 (58-65)	65 (58-69)	
Incidental GIST	28/60 (43.3%)	18/38 (47.4%)	12/22 (54.5%)	0.935
Symptomatic GIST	34/60 (56.6%)	20/38(52.6%)	14/22(63.6%)	

mal tumors of gastrointestinal tract^{1,2} Their precise definition as a distinct tumor entity is relatively recent. They were firstly identified as “bizarre leiomyomas”³ and only in 1983 they were properly classified by Mazur and Clark^{4,5}. Their supposed origin is from a common precursor cell, which gives rise to the interstitial cells of Cajal as a result of activating mutation in one of the receptor protein tyrosin kinase KIT or platelet-derived growth factor receptor alpha (PDGFRA)^{6,7}. Their diagnosis is often incidental, GISTs with a diameter of less than 1 cm (micro-GIST) occur in roughly one of three adults and are generally considered benign².

They can arise anywhere but their outmost frequent origin site is stomach (50-70%).

The management of patients with GIST rapidly changed after the introduction of tyrosine kinase inhibitors (TKIs), such as imatinib mesylate¹⁰⁻¹².

However surgical resection is the mainstay once the diagnosis of GIST has been established, and the goal of surgery is complete resection while avoiding tumor rupture and achieving negative margins in the treatment of gastric non metastatic GIST¹¹⁻¹⁴. Traditional surgical treatment of gastric GIST involves the open approach but in the last two decades laparoscopy gained room even in this field^{14,16,17}.

Comparing the two different approach the aim of this study is to demonstrate the safety and feasibility of the minimally invasive treatment still ensuring the same oncological principles than open approach. Short term and long terms outcomes

The lower morbidity and mortality related to this kind of surgery should be the spur to consider it the treatment of choice in the management of gastric GISTs.

Materials and Methods

This study enrolled 60 patients who underwent surgery for gastric GIST from 2004 to 2013 at Clinica Chirurgica of Università Politecnica delle Marche.

They have been divided into two groups: those who underwent open surgery (22, OG) and those in which laparoscopic surgery was performed (38, LG).

Mean age was 60.88 years (45-70) in laparoscopic group (LG) and 64.36 years (53-81) in open group. There was no significative difference between the two group for age (p= 0.466) and sex (p= 0.699).

Clinical presentation was heterogeneous. Symptomatic patients showed variably fatigue secondary to anemia, intraluminal gastrointestinal bleeding, abdominal pain, abdominal mass, vomiting and syncope. The most common symptom in both groups was melena (21.43 %), followed by anemia (17.8%) and abdominal pain (10.7%). One patient showed abdominal mass, hematemesis and weight loss.

In 26 asymptomatic patients (43.3%) gastric GISTs were detected incidentally during abdominal exploration, endoscopy, or radiologic imaging (Table I).

Patients underwent preoperative Computerized Tomography (TC), Magnetic resonance (MR) and/or positron emission tomography (PET) to exclude metastasis or synchronous tumors. Patients with metastatic disease and those that underwent to palliative surgery were excluded from this study. Other exclusions criteria were American Society of Anesthesiologists (ASA) fitness grade III-IV and follow up shorter than 48 months.

Diagnosis was made in many cases post-operatively after pathological and immunoistochemical analysis. Endoscopic ultrasound guided fine needle aspiration (EUS-FNA) allowed preoperative diagnosis of GIST in 4 patients.

All patients were properly informed about the risks and gave their consensus for surgery.

Operative data included operative time, intraoperative complications and conversion.

Surgical specimens were analyzed to evaluate margins, cellular density and mitotic index.

Tumors were classified in three categories according to histological features that are spindle cell, epithelioid type and mixed spindle cell and epithelioid type⁷

Immunoistochemical analysis included CD117, CD34, smooth cell actin (SMA), DOG1, Desmin and S100 protein.

Expression of CD117 and CD34 was considered as indicative for GIST^{4,5}.

GISTs were sorted in very low, low, intermediate and high risk tumours according to Fletcher's criteria⁸.

Time for gastrointestinal function recovery, removal of nasogastric tube, post-operative complications, peri-operative mortality and length of hospital stay were evaluated.

All Patients underwent follow-up with Computerized Tomography (TC) and/or Magnetic Resonance (MRI) repeated every year

Mean follow up period was (mean 83.5 months, range= 49-120).

Continuous data are reported as mean and minimum and maximum values in brackets. Statistical difference between the two groups were assessed by Student's t test for continuous data and Fisher's exact test for categorical data. A p value < 0.05 was considered statistically significant.

LAPAROSCOPIC TECHNIQUE

The patient was placed supine in anti Trendelenburg position. Pneumoperitoneum was achieved with the Hasson open technique until 12-14 mmHg. The first trocar was supraumbilical followed by other three trocars placed under vision at the upper right quadrant (5mm), at the upper left quadrant (10 mm) and right flank (10 mm). Resection technique is different based on tumor site and dimension. If the GIST showed an exophytic growth, it was sufficient to use endoGIA on the base of the tumor.

Two tumors with an intramural growth required intraoperative ultrasound to precisely display the lesion before a wedge resection of the body of the stomach was performed. In one patient with a GIST with endophytic growth from posterior wall of the stomach an anterior gastrotomy was performed and the lesion was excised by endoGIA.

All tumors was extracted with a plastic endocatch trough an extended umbilical incision.

Results

R0 resection was achieved in all patient except one in the laparoscopic group in which retracted margin did not allowed a clear pathological examination.

TABLE II - Operative data

Variables	Patients (n=60)	LG (n=38)	OG (n=22)	p
Time (min)				0.0173
Mean (range)	96.42 (50-150)	82.4 (50-110)	117(85-150)	
Median (1°-3° percentile)	95(73.75-116.25)	90 (55-105)	115 (90-145)	
Intraoperative complications	0/28	0	0	1.000
Conversion		6/38 (15.7%)		
Blood loss				0.173
Mean	75.92±232.61	3.35±68.33	150±68.33	
Site				0.758

There were no tumor rupture or other intraoperative complications. Six patients (15.7%) required conversion to open surgery due to difficulties for site or tumor size. In OG surgical procedure included gastric resection (11), gastrotomy (3), total gastrectomy (2) and distal subtotal gastrectomy (6).

The operating time was significantly lower (p=0.0173) in LG (82.4 min) than in OG (117.8 min).

Blood loss did not differ statistically between two groups (p= 0.173) (Table II).

LG and OG differed statistically in time of removal of nasogastric tube (2.17 Vs 2.75, p= 0.045), and time of re-alimentation (3.35 Vs 5.18, p= 0.001).

There were no complications in LG while 4 patients (6.6%) in the OG showed postoperative bleeding and required blood transfusions (Table III).

In many patients diagnosis was made post-operatively; only 4 (6.6%) patients underwent surgery with a pre-operative histological diagnosis of GIST, as had been reported by other authors².

The overall mean dimension was of 4.75 cm (range= 2-13). Mean tumor diameter was 6.29 (range=5-12) in OG and 3.7 (range=2-7.5) in LG.

Thirty-four (56.7 %) were spindle cells GISTs, 12 (20 %) hepiteliod type GISTs and 14 (23.3%) mixed type GISTs.

There was no statistically difference between two groups for mitotic index (p= 0.265) nor for risk class (p=0.998). Twenty-four patients present very low risk tumors (40%), 30 low risk tumors (50%), 4 patients middle risk tumors (6.6 %) and 2 high risk tumors (3.3%) according with Fletcher criteria.

None of the patients underwent neo-adjuvant nor adjuvant chemotherapy.

In our series we did not observe recurrence or metastasis at mean follow up period of 51.98 (range= 49-120 months) (Table IV).

Discussion

In the last two decades the surgical management of gastric GIST we observed the introduction of minimally invasive techniques in surgical management of gastric GIST, traditionally managed by open approach^{16,19}.

TABLE III - Post-operative data

Variables	Patients (n=60)	LG (n=38)	OG (n=22)	p
Post-operative complications	4/60 (6.7%)	0	4/22 (18.2%)	0.045
SNG removal				
Mean \pm SD	2.75 \pm 1.94	2.17 \pm 1.91	3.63 \pm 1.69	
Median (1°-3° percentile)	3 (1.75-4)	2 (0-3)	3 (2.5-4.5)	0.012
First flautulence				
Mean \pm SD	3.46 \pm 1.31	3 \pm 1.32	4.18 \pm 0.98	
Mediana (1°-3° percentile)	3.5 (3-4)	3 (3-4)	4 (3.5-5)	0.001
Realimentation				
Mean \pm SD	4.07 \pm 1.67	3.35 \pm 1.61	5.18 \pm 1.08	
Median (1°-3° percentile)	4.5 (3-5)	3 (2-5)	5 (5-6)	0.014
Hospital stay				
Mean (range)	7.71 (4-15)	7 (4-10)	8.82 (5-15)	
Median (1°-3° percentile)	8 (6-9.25)	7 (6-9)	9 (8.5-10)	
Follow up				
Mean (month)	51.98 (49-120)	51(49-115)	55.72 (49-120)	
Recurrence	0	0	0	

TABLE IV - Tumor's characteristics

Variables	Patients (n=60)	LG (n=38)	OG (n=22)	p
Dimension (cm)				0.200
Mean (range)	4.75 (2-13)	3.7 (2-7.5)	6.29 (3-13)	
Median (1°-3° percentile)	4(3-5)	3.5 (3-4)	4.5 (3.75-5.75)	
Mitotic index(50 HPF)				0.265
<5	30/60 (50%)	16/38(42.1%)	8/22 (36.4%)	
5-10	16/28 (26.7%)	7/38 (18.4%)	9/22 (41%)	
>10	4/60 (6.6%)	2/38 (5.3%)	2/22 (9%)	
Margins (R0)	27/28 (99.42%)	16/17 (94.11%)	11/11 (100%)	1.000
Risk assesment				0.998
Very low risk	6/60 (107%)	5/38 (13.2%)	1/22 (4.5%)	
Low risk	30/60(50%)	20/38 (52.6%)	10/22 (45.4%)	
Intermediate risk	22/60(38.3%)	13/38 (21.7%)	10/22 (45.4%)	
High risk	2/60(3.3%)	1/38 (2.6%)	1/22 (4.5%)	
Histology				0.054
Spindle cells	34/60 (56.6%)	24/38 (63.1%)	10/22 (45.4%)	
Hepitelioid type	10/60 (17.8%)	8/38 (21%)	2/22 (9%)	
Mixed type	16/60 (26.7%)	6/38 (15.8%)	10/22 (45.4%)	

Lukaszczuk et al. in 1992¹⁷, followed by many other authors, proposed laparoscopic wedge resection as the optimal approach to obtain a complete resection of gastric GIST with low morbidity¹⁹⁻²⁸.

In several retrospective series comparing laparoscopic and open approaches, the laparoscopic approach was found to be associated with better short-term and comparable longterm outcomes than those of open surgery¹⁷.

Laparoscopic approach can be easier for gastric GIST than for tumors located in other sites for their peculiar characteristics as a mainly exophitic growth and tendency to not infiltrate adjacent structures, that allows to

perform an organ sparing surgery without the necessity of wide resection margins¹⁴.

As submucosal and lymphatic spread is rarely observed in gastric GISTs making them easily maneageable with a local or wedge resection¹⁴.

With the advent of laparoscopy various controversies arises for management of these tumors²⁹⁻³¹.

The 2004 European Society for Medical Oncology (ESMO) Consensus Conference on GISTs recommended that laparoscopic surgery might be acceptable in cases of small (< 2 cm) intramural tumors.

From then various reports demonstrated the safety and

feasibility of laparoscopic surgery for gastric GIST and led to the development of new guidelines.

ESMO guidelines recommend that laparoscopic excision follow the principles of oncologic surgery and a laparoscopic approach in larger tumors because of the higher risk of tumor rupture and peritoneal seeding. Laparoscopic resection was the treatment of choice in several series, in which it was demonstrated to be feasible and safe, even for tumors > 5 cm, when performed by an experienced operator.

The 2007 National Comprehensive Cancer Network (NCCN) Guidelines® emphasized the expanding role of laparoscopy and its safety when performed by experienced surgeons. Nowadays laparoscopy is recommended for tumors \geq 5 cm with the use of hand-assisted laparoscopy for larger tumors³¹⁻³³.

Compared with open surgery the laparoscopic approach is significantly better in term of short term outcomes. Patients showed an early recovery of gastrointestinal function resulting in a significantly shorter time of hospitalization.

We did not consider tumor size as a contraindication to the minimally invasive approach and we perform laparoscopic wedge resection for tumors of 7.5 cm diameter.

Even the location was not discriminating between the two techniques. It did not exist a statistically significant difference in the origine site between the two groups and even tumors arising from the gastroesophageal junction or the pyloric outlet underwent laparoscopic resection.

Tumor characteristics such as size and site have been important sometimes to prefer the open approach but they did not statistically differ between the two groups. GISTs arising from the stomach are known as having a better prognosis than GISTs at other sites. However tumour rupture during surgery is a negative prognostic factor. The estimated risk of recurrence for a tumor with no rupture, a diameter of \geq 5 cm, and a mitotic count of \geq 10 high-power fields (HPFs) ranged between 20% and 26%²⁶.

Because GISTs are highly friable, strict no-touch technique and tumor retrieval through a plastic bag should be considered mandatory to minimize the risk of peritoneal dissemination.

Oncological results evaluated as disease free survival and recurrence rate resulted equivalent between the two techniques in a follow up superior to five^{27-29,34}.

The absence of intra and post-operative complications in this series shows as laparoscopic approach can be considered safe and effective in the treatment of gastric GISTs like open surgery.

Conclusions

Laparoscopic wedge resection is a safe and feasible approach for gastric GISTs with oncological results comparable to open surgery.

Considering the advantages associated with laparoscopic surgery, a minimally invasive approach should be the procedure of choice in the case of small and even medium-sized tumors, reserving open surgery in cases where size or location of the tumor make laparoscopy not practicable.

However this technique required a skilled surgeon in this procedure.

Riassunto

I Tumori Stromali Gastrointestinali (GIST) sono tumori rari ma rappresentano le neoplasie mesenchimali più frequenti del tratto gastroenterico. Insorgono più frequentemente a livello gastrico e la resezione chirurgica rappresenta ad oggi la terapia di scelta per la malattia primitiva non metastatica. Le loro caratteristiche peculiari di crescita e la scarsa tendenza ad invadere gli organi adiacenti li rendono particolarmente maneggevoli con un approccio miniminvasivo. Presentando la nostra esperienza vogliamo dimostrare l'applicabilità e la sicurezza della laparoscopia nel trattamento dei GIST gastrici ed i suoi vantaggi rispetto alla chirurgia tradizionale laparotomica.

Abbiamo confrontato i risultati derivanti dall'analisi retrospettiva di una serie di 60 pazienti sottoposti a chirurgia per GIST gastrico dal 2004 al 2014 nella Clinica Chirurgica dell'Università Politecnica delle Marche. I pazienti sono stati suddivisi in due gruppi a seconda del trattamento chirurgico utilizzato, laparoscopico e o laparotomico. I criteri di esclusione sono stati la presenza di malattia metastatica e l'esecuzione di chirurgia a scopo palliativo.

La diagnostica preoperatoria ha previsto l'esecuzione di ecoendoscopia, ago aspirato, TC/RMN o PET ma nella maggior parte dei casi la diagnosi definitiva è stata postoperatoria e basata sull'analisi immunohistochimica. Sono stati diagnosticati come GIST i tumori mesenchimali che mostravano positività per i marcatori CD 117 e CD34.

I GIST sono stati quindi suddivisi in quattro gruppi prognostici sulla base delle loro caratteristiche anatomopatologiche, in accordo con quanto descritto da Fletcher nel suo nomogramma prognostico.

Nessuno dei pazienti è stato trattato con Imatinib preoperatoriamente. Tutti i pazienti sono stati sottoposti a follow up con TV e/o RM ripetute annualmente.

Dei 60 pazienti arruolati nello studio 22 (36.7%) sono stati trattati con tecnica open, 38 (63.33%) con tecnica laparoscopica e uno di questi con tecnica robotica tramite il sistema robotico da Vinci®.

Non sono state notate differenze significative per quanto riguarda età, sesso, sintomatologia e dimensioni della massa e caratteristiche anatomopatologiche all'esame istologico definitivo tra i due gruppi. L'età media alla diagnosi è stata di 64 anni (range= 45-71). I pazienti rife-

rivano una sintomatologia variabile comprese astenia ed anemia, sanguinamento intraluminale, dolore addominale, senso di massa, vomito e sincope.

In 26 pazienti (43.3%) la presenza di un GIST gastrico è stato un reperto occasionale in seguito a procedure endoscopiche o radiologiche eseguite per altri motivi. La dimensione media era di 4.75 cm (range= 2-13).

Sono stati registrati tempi operatori inferiori in laparoscopia rispetto alla tecnica laparotomica (82.4 versus 117.8 min). Una differenza statisticamente significativa è stata inoltre osservata per quanto riguarda il tempo di rimozione del sondino nasogastrico, il tempo necessario alla ricanalizzazione ai gas e alla rialimentazione e la durata della degenza ospedaliera.

Non abbiamo osservato complicanze intra o post operatorie nei pazienti trattati con tecnica laparoscopica mentre in 4 pazienti sottoposti a laparotomia abbiamo riscontrato anemizzazione con necessità di trasfusione. Non sono state riscontrate recidive o metastasi in tutto il periodo di follow up (range= 49-120 months).

Il nostro studio dimostra come la laparoscopia sia un'alternativa efficace alla chirurgia tradizionale nel trattamento dei GIST gastrici. La tecnica minvasiva offre numerosi vantaggi soprattutto nell'immediato decorso post-operatorio che si traducono in una minore degenza ospedaliera. I risultati oncologici delle due tecniche sono invece sovrapponibili.

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