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Robotic-Assisted Gastric GIST Resection: A Single Center Experience

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1. Abstract

1.1. Aims: Gastrointestinal Stromal Tumors (GISTs) are the most common mesenchymal tumors, representing 1-3% of all gastrointestinal cancer. Surgical resection is the only curative treatment. Minimally invasive approaches such as laparoscopic and robotic-assisted resections for gastric GISTs have proved to be oncologically and surgically safe. We report here a case series of robot-assisted gastric GISTs resections in our center.

1.2. Methods: We performed a retrospective analysis of all gastric GISTs resected between 2007 and 2019 at the Geneva University Hospital, Switzerland.

1.3. Results: Nineteen patients underwent robot-assisted gastric resection for GISTs, twelve females and seven males. Median age was 59 years (range 38-79) and median BMI was 27.5kg/m^2 (range, 18.6-41.3). Median tumor size was of 5 cm (range, 1.8-9). Thirteen cases were localized at the posterior wall and seven were proximal (near the cardia). All tumors were completely resected (R0). We noted one conversion to open resection because of a positive margin requiring a subtotal gastrectomy. Median operative time was 157 minutes (range, 90-436). We reported no postoperative complications and no mortality within 90 days after surgery. The median follow-up was 22.5 months (range, 1-139) without tumor recurrency.

1.4. Conclusions: Our case series confirm that robotic-assisted resection is safe and offers satisfactory oncological results for gastric GISTs.

2. Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal (GI) tract and represent 1% of all primary GI cancer [1]. They are derived from interstitial cells of Cajal and can arise along the entire GI tract [2]. They are mostly found in the stomach (60%) and in the small intestine (30%) but can also be seen in the omentum, the mesentery, and the peritoneum [1-3]. Because tumors are friable and highly vascularized, GI bleeding is one of the most common initial symptoms. The diagnosis is made based on the microscopic appearance, classically with the presence of spindle and/or epithelioid cells, and on immunohistochemistry analyses [2, 4]. Nearly 95% of GISTs are positive for KIT protein (CD 117), 94.4% for DOG-1, and 70% for CD 34. Assessment of DOG-1 positivity is very useful to establish diagnosis in KIT-negative GISTs [2, 5]. GIST development is most commonly the result of activating mutations in the *Kit* and in the platelet-derived growth factor receptor alpha (*PDGFRA*) genes at a frequency of 80% and 7.2%, respectively [6-8]. Those activated tyrosine kinase receptors are the targets of the tyrosine kinase inhibitors.

GISTs are locally invasive tumors with potential for metastasis depending on the localization, the mitotic rate, and the size [9]. For instance, gastric GISTs are less aggressive than small intestine GISTs [2]. Since the discovery and the use of tyrosine kinase inhibitor, patients with inoperable tumors or with high risk of recurrence can benefit from a neoadjuvant and/or adjuvant treatment. Despite this advance, surgical resection remains the gold standard for curative treatment [10-12]. Over the last few decades, minimally invasive surgery has improved and is now well accepted in oncological surgery as a safe approach for many types of abdominal malignancies, such as upper gastrointestinal tumors [13, 14]. Several studies have reported the feasibility of laparoscopic and robotic-assisted laparoscopic GIST resection and proved it to be oncologically safe [10, 15-17]. Moreover, the lack of a need for extended resection and excision of lymph nodes make GISTs very good candidates for a minimally invasive approach. Thanks to 3D vision and the full range of instruments' mobility, robotic-assisted laparoscopy has proved its efficacy and is a very useful tool. We report here our robotic gastric GIST resection series in our center.

3. Material and Methods

We performed a retrospective analysis of all gastric GISTs resected robotically between 2007 and 2019 at the Geneva University Hospitals, Switzerland. Patient characteristics such as age, gender, body mass index (BMI), ASA score, initial symptoms, and surgical history were collected as well as tumor characteristics (size, localization). Tumors were categorized between anterior or posterior wall localization and separated into three categories: proximal (fundus or cardia), corpus, or distal (antral). Tumor size was based on the final pathological report. Information related to the surgery (duration, blood loss, type of resection, conversion rate) were also analyzed. The surgeon learning curve was assessed by comparing the mean operating time between the 8 first patients and the last 11 patients. Operation time represented the time between the first incision and the last closing skin suture. Significant blood loss was defined by the need for a perioperative transfusion or loss ≥500mL. Histology findings regarding tumor margins, histological markers, numbers of mitoses, as well as the indication for adjuvant treatment were also taking into account. Indication for adjuvant therapy was based on the Miettinen classification, reporting the risk of recurrence depending on the size of the tumor and the number of mitoses for 50 fields. The risk of recurrence was expressed as very low, low, intermediate, and high. Assessment of *Kit* and *PDGFR-alpha* mutations had been performed since 2016 on patients with a Miettinen classification characterized as low or higher. Post-surgical complications were assessed by the Dindo–Clavien classification [18], and mortality rate was reported at 30 and 90 days post-surgery.

4. Quality of Life Assessment

The actual and one-year post-surgery quality of life assessment were performed using the EORTC QLQ-C30 3.0 form. This quality of life assessment tool was developed for oncological patients and evaluates the global health status (GSH), five functional scales (physical, role, emotional, cognitive, and social), and nine symptom items. Each patient was contacted by phone, allowing us to fill in the EORTC QLQ-C30 form [19-24] to evaluate the follow-up and the eventual recurrence of the disease. Data obtained were compared to previously published results from a reference population of 7802 healthy individuals (age ranging from 40 to 80 years; 52% males and 48% females) (ref11). Results are expressed as median with range or mean with standard deviation. The Mann–Whitney test was used to compare means. A p-value of ≤ 0.05 was considered statistically significant. Graph Pad prism 8.0 software was used for the analyses.

This study has been approved by the local ethics committee.

5. Patient Installation and Trocars' Position

The da Vinci Robots S, Si and Xi from Intuitive® were used. Patients were anesthetized and orotracheally intubated. After patient installation in the dorsal decubitus and placement of sterile fields, incision marks were drawn on the abdomen. The four robotic trocars were placed 8 centimeters from each other on a horizontal line going through the umbilic (Figure 1). Two 8-mm and two 12-mm trocars were used. The Air Seal port, used for the assistant, was placed 8 centimeters under the umbilic on the left side of the abdomen midline. The last trocar was 5 millimeters, used for the liver retractor and placed 17 centimeters over the umbilic on the midline. Next, the da Vinci robot was docked on the right side of the patient. Exophytic tumors that protruded in the abdominal cavity were easily located, and simple wedge resections were performed. Tumors located in the gastric wall without external protrusion or with intra-gastric protrusion were either marked by an ink tattoo during a previous gastroscopy or located by perioperative gastroscopy.

6. Results

Patient and tumor characteristics are summarized in (Table 1). Between 2007 and 2019, nineteen patients, thirteen (65%) females and seven (35%) males, had a robotic-assisted gastric GIST resection in our center. The median age was 59 years (range 38–79) and median BMI was 27.5kg/m^2 (range, 18.6–41.3). Most frequent initial symptoms reported were asthenia, epigastric pain, melenic stool, and hematemesis. Five patients (26.3%) were asymptomatic, and their GIST diagnoses were the result of incidental findings. Nine patients (47.4%) were admitted in an emergency for active bleeding. We found thirteen tumors (68.4%) localized on the posterior wall and six (31.6%) on the anterior wall of the stomach. Seven tumors (36.8%) were proximal, four (21.1%) localized at the fundus, and three (15.8%) at the cardia. Seven tumors (36.8%) were found in the corpus, and five (26.4%) were distally localized at the antrum. Partial gastrectomy was performed in eighteen cases. We reported one conversion (1/19 (5.3%)), patient 3, who needed a subtotal gastrectomy after confirmation at the intra-operative biopsy of a positive margin.

The median operative time was 157 minutes (range, 90–436). The mean operative time of the first eight patients and the last eleven patients were respectively 246.6 ± 123.3 and 171 ± 92.9 minutes (p = 0.310; (Figure 2). No significant blood loss or perioperative complications were reported. Histology findings confirmed that all tumors were completely resected (R0). Median tumor size was 5 cm (range, 1.8–9), and the median mitosis number for 50 fields was of 3 (1–83). Recurrence risk according to the Miettinen classification showed that five patients (26.3%) presented a very low risk, two (10.6%) a low risk, seven (36.8%) an intermediate risk, and five (25%) a high risk. Tumors' positivity for CD 117 and CD 34 were 88.9% and 68.4%.

Assessment for *Kit* and *PDGFR-alpha* gene mutations was performed on seven patients' tumors, and four (57.1%) presented a *Kit* gene mutation and three (42.9%) presented a *PDGFR-alpha* mutation. Tumor markers for each patient are summarized in Table 2.

Adjuvant therapy with imatinib was indicated for the five patients with a high risk of recurrence according to the Miettinen score. After exclusion of the patients who refused or who were considered too old for the treatment, only one patient received imatinib for a three-year duration. The median length of hospital stay was 7 days (range, 4-18).

We reported no postoperative complications and no mortality within 90 days after surgery. Median follow-up was 22.5 months (range, 1–139) without tumor recurrence.

Data from the EORTC QLQ-C30 form are presented in Figure 3. Four patients were lost to follow-up and could not be included in the quality of life assessment. Globally, we observed better results in our population than in the reference population, with statistically significant differences for all functional scales with the exception of cognitive function. In the symptom items, patients in our study presented significantly less fatigue, pain, dyspnea, and insomnia than the reference population. Differences inside our study between one year after surgery and the last follow-up were negligible.

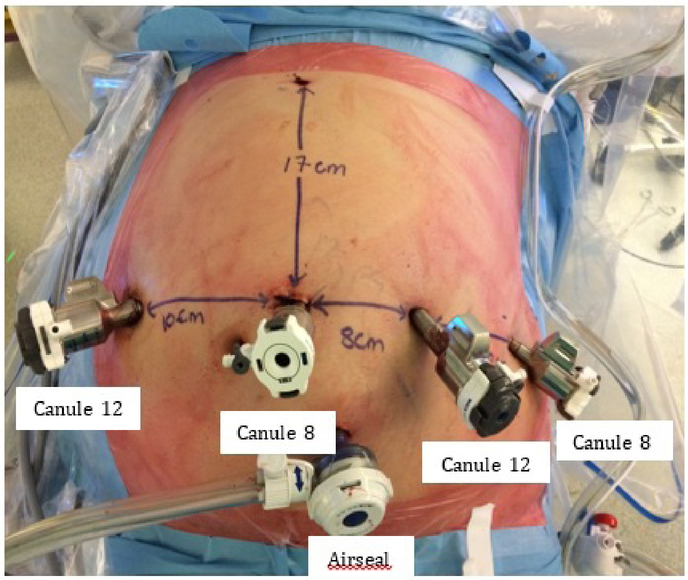

Figure 1: Patient installation and trocars position

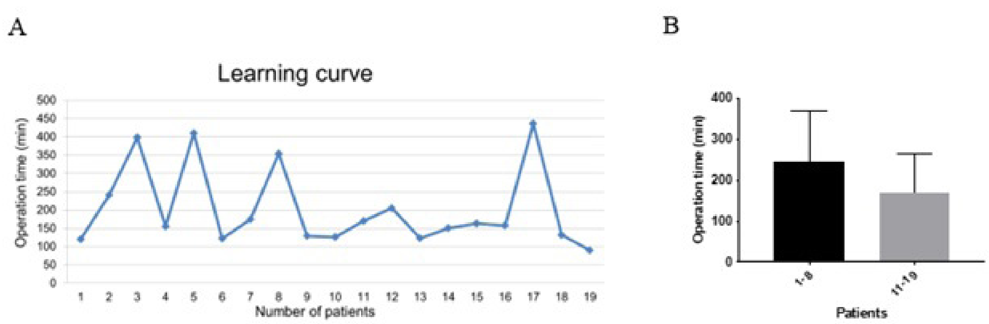

Figure 2: Learning curve. **A.** Operation time per patient. **B.** Duration comparison between the first 8 and last 11 patients.

	GIST 1 year (*n*=14)	GIST today (*n*=14)	Normal value (*n*=7802)	*p* value		
	Mean score (SD)	Mean score (SD)	Mean score (SD)	1y vs Today	1y vs Normal	Today vs Normal
GHS	79.76 (20.1)	80.95 (19.5)	71.2 (22.4)	0.875	0.135	0.084
Physical function	98.09 (4.1)	99.05 (3.6)	89.8 (16.2)	0.51	0.0001	<0.0001
Role function	97.62 (6.1)	97.62 (6.1)	84.7 (25.4)	0.999	0.0001	<0.0001
Emotional function	92.26 (11.5)	94.05 (9.5)	76.3 (22.8)	0.66	0.0002	<0.0001
Cognitive function	94.05 (22.3)	94.05 (22.3)	86.1 (20.0)	0.999	0.205	0.205
Social function	96.43 (7.1)	96.43 (7.1)	87.5 (22.9)	0.999	0.0004	0.0004
Fatigue	9.52 (23.0)	7.14 (18.3)	24.1 (24.0)	0.764	0.034	0.004
Nausea	3.57 (7.1)	3.57 (7.1)	3.7 (11.7)	0.999	0.947	0.947

Pain	5.95 (12.4)	4.76 (10.2)	20.9 (27.6)	0.784	0.0006	<0.0001
Dyspnea	2.38 (8.9)	2.38 (8.9)	11.8 (22.8)	0.999	0.002	0.002
Insomnia	9.52 (15.6)	9.52 (15.6)	21.8 (29.7)	0.999	0.011	0.011
Appetite	7.69 (14.6)	5.13 (12.5)	6.7 (18.3)	0.635	0.804	0.647
Constipation	4.76 (12.1)	4.76 (12.1)	6.7 (18.4)	0.999	0.56	0.56
Diarrhea	4.76 (12.1)	4.76 (12.1)	7.0 (18.0)	0.999	0.501	0.501
Finances	4.76 (12.1)	4.76 (12.1)	9.5 (23.3)	0.999	0.168	0.168

Figure 3A: Global health score (GHS), functional scales and symptom scales of the EORTC QLQ C-30 in patients one year after surgery and the day they were contacted for follow-up. Data are compared with normal values provided by the EORTC [24]. Data are expressed in means (standard deviations)

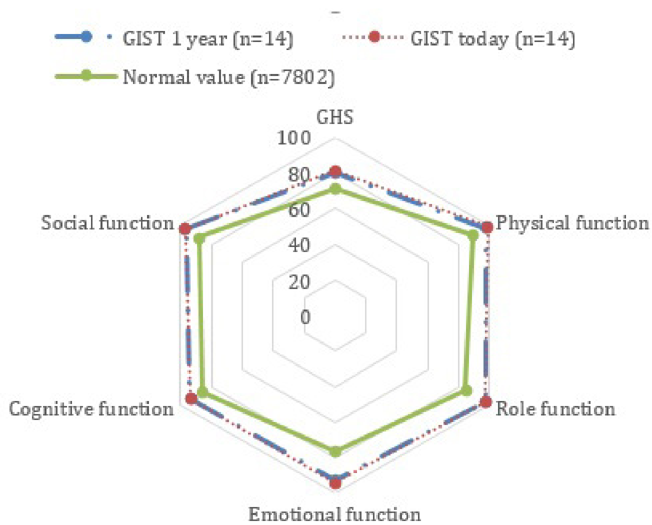

Figure 3B: Spider graph representing the data from the EORTC QLQ C-30 for the patients one year after the surgery, at the moment of the last follow up in comparison with the reference population

Table 1: Patient and tumor characteristics

Variables	Patients (19)
Patient characteristics	
Age, y (median, range)	59 (38-79)
Sexe, female (%)	12 (63.2)
BMI, kg/m2 (median, range)	27.5 (18.6-41.3)
ASA score, n (%)	
I	1 (5.3)
II	12 (63.2)
III	6 (31.5)
Previous surgery (%)	8 (42.1)
Operation time, min (median, range)	157 (90-436)
Follow up, months (median, range)	8 (1-115)
Tumor characteristics	
Size cm, (median, range)	5 (1.8-9)
Localization, n (%)	
Posterior wall	13 (68.4)
Proximal	7 (36.8)
Corpus	7 (36.8)
Distal	5 (26.4)
Conversion (%)	1 (5.3)
R0 resection (%)	19 (100)
Mitosis for 50 fileds (median, range)	3 (1-83)
Miettienen score, n (%)	
Very low	5 (26.3)
Low	2 (10.6)
Intermediate	7 (36.8)
High	5 (26.3)
Histological markers	
Kit gene mutation, n (%)	4 (21,1)
CD117 positive, n (%)	16 (84,2)
PDGFR-alpha, n (%)	3 (15,8)

Table 2: Histological tumor markers.

	Patients																			
Histological markers	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**Total**
CD 117	+	-	-	+	+	+	/	+	+	+	+	+	+	+	+	+	+	+	+	16/18 (88.9%)
CD 34	+	-	+	+	-	/	/	+	+	+	+	+	+	-	+	+	+	/	+	13/16 (81.3%)
AML	+	+	+	+	-	-	-	-	-	-	-	+	-	-	-	+	-	+	-	7/19 (36.8%)
DOG-1	/	/	/	/	/	/	+	+	+	+	+	+	+	+	+	+	+	+	+	13/13 (100%)
Kit mutation	/	/	/	/	/	/	/	-	+	/	-	+	+	/	/	+	-	/	/	4/7 (57%)
PDGFR-Alpha	/	-	/	/	/	/	/	+	-	/	+	-	-	/	/	-	+	/	/	3/8 (38%)

Makers are represented if present in the tumor by "+", if absent by "- "and if no information were available by "/". AML = Acute myoloid leukemia, DOG-1 = discovered on gastrointestinal stromal tumors protein 1.

7. Discussion

GISTs are rare digestive tumors that most of the time require a surgical resection in order to be cured. Because GISTs don't usually invade lymph nodes or involve adjacent organs, there is no need for wide resection of uninvolved tissue with systematic lymph node resection, as is recommended for gastric cancer [2, 25, 26]. In order to be curative, a total resection with negative microscopic margins (R0) is essential [27]. There is actually no consensus to determine the size of the margin to be respected, but 2 centimeters seems to be accepted in the literature [15, 28]. For those reasons, and because most gastric GISTs are exophytic tumors, they are perfect candidates for laparoscopic or robotic-assisted laparoscopic resections.

In 2007, the National Comprehensive Cancer Network (NCCN) edited guidelines indicating the feasibility of laparoscopic GIST resection for tumors <2cm [2]. After the publication of several studies showing GIST resections over 2cm, those guidelines were modified in 2010, and minimally invasive resections were recommended for tumors of 5cm or less [27]. The European Society for Medical Oncology (ESMO) recently published guidelines that discouraged laparoscopic resection for large tumors [29]. The main reported risk for laparoscopic resection was tumor rupture with intra-peritoneal dissemination, resulting in a worse prognosis.

The main limitations of laparoscopy in gastric GIST resection are non-visible tumors, proximal or distal tumors requiring precise dissection (e.g., near the esophagus) and reconstruction without causing stenosis, and large tumors making the mobilization of the GIST risky and complicated. It is in those cases that robotic-assisted laparoscopy is very useful. It allows precise dissection and reconstruction with 3D vision and full-range-of-motion instruments.

We presented 19 gastric GIST resections of tumors ranging from 1.8 to 9 cm with 100% R0 resections. We confirmed, as in the literature, that minimally invasive methods for gastric GIST resection, even with tumors larger than 5 cm, are safe and feasible. Moreover, almost 40% of our cases had proximal tumors, and about 70% percent were localized on the posterior wall, and no complication or recurrence was reported.

Mean operating time in the first 8 patients showed significant inconsistency and long duration that faded away by the last 11 patients. By looking at the learning curve, we can see that with a small number of patients, a lot of progress has been made in terms of duration, with more consistency. With the exception of patient 17, the last 10 patients were in a similar operation time range that was significantly better than that of the first 8 patients. It is noteworthy to mention that the resections were not performed by a single surgeon. Therefore, the reported results reflect more the institutional learning curve, taking into account not only the surgeon, but the operating theater staff as well. However finally, because most gastric GISTs are visible exophytic lesions, they are perfect candidates for surgical robot education.

Data obtained from the EORTC QLQ-C30 in our group showed a very good quality of life one year after surgery as well as at the last follow-up. This reflects the benefits of minimally invasive surgery with small incisions, short hospital stays, and the absence of the need for large resection with extensive dissection. The fact that our group presented better results than the reference healthy population is most likely explained by the huge difference in sample sizes. Regardless, our study showed very good results in terms of recurrence-free survival and quality of life.

The main limitations of this study are the small number of patients and its retrospective aspect. As mention above, gastric GISTs are uncommon disease and therefore, having a large cohort is complicated, especially in a small country such as Switzerland. In addition, minimally invasive resection for large GISTs was not recommended until recently, reducing furthermore the number of patients.

8. Conclusion

This case series confirms that robotic-assisted laparoscopy is a valid method for gastric GIST resection, especially for proximal, distal, large, and fragile lesions. Tumor size shouldn't limit the use of this minimally invasive method, but very large lesions should be analyzed case by case regarding the localization and signs of tumor necrosis in order to avoid tumor rupture and intra-abdominal dissemination.

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