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Update on Laparoscopic Treatment of Gastrointestinal Stromal Tumors

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Abstract

Laparoscopic surgery and tyrosine kinase-inhibitor (TKI) therapy are frequently used to treat gastrointestinal stromal tumors (GISTs). The purpose of this review was to analyze the published data on minimally invasive treatment of GISTs, with special focus on tumor location and on the possible role of laparoscopy in association with imatinib mesylate therapy in the treatment of advanced forms. The MEDLINE® and Embase® databases were searched for potentially eligible English-language studies published through June 30, 2015. Laparoscopic surgery can be considered a treatment option for GISTs at all locations. Most gastric GISTs are suitable for laparoscopic wedge resection (44-100% in recent series). Gastric GISTs in difficult-to-treat areas may benefit from innovative approaches such as transgastric or intragastric resection. Few data are available for small-bowel and colonic GISTs, although laparoscopic resection complying with the oncologic principles seems feasible and safe with reported morbidity and mortality rates of 3.8-6.7% and 0%, respecively. Primary resection of large rectal GISTs carries a risk of recurrence up to 40%. To improve long-term results and reduce the invasiveness of surgery in this setting, as in other difficult-to-treat areas, neoadjuvant imatinib therapy should be considered. In selected cases, the combination of imatinib mesylate therapy and laparoscopy can minimize surgical trauma. The appropriate adoption of laparoscopic surgery and TKI therapy can reduce surgical trauma and optimize long-term results.

Keywords: GIST; Gastrointestinal; Laparoscopic surgery; Tyrosine kinase-inhibitor therapy

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. They are quite rare, representing 0.3–3% of all gastrointestinal tumors [1]. At presentation, potential dimensions and malignancy vary with tumor location, size, and mitotic count [2-4]. GISTs with a diameter of less than 1 cm (micro-GIST) occur in roughly one of three adults and are generally considered benign [5,6]. Conversely, large GISTs with high mitotic counts, typically occurring in the liver and abdominal cavity, have high rates of recurrence after surgery alone or in combination with tyrosine kinase-inhibitor (TKI) therapy [7-9].

GISTs may occur anywhere along the gastrointestinal tract. They are located mainly in the stomach (50–70%) and small bowel (20–30%), but they can also occur in the esophagus (5%), the colon and rectum (5%), and occasionally in the omentum, mesentery, or retroperitoneum [10].

Although no randomized controlled trials have been published comparing laparoscopic and open resection, laparoscopic surgery is widely performed and is considered safe for small GISTs [11,12]. Several case series on primary laparoscopic treatment of gastric GISTs have been published [13,14], but data on GISTs in other locations, or those treated in association with TKIs, are scarce [15,16].

The purpose of this review was to analyze the published data on minimally invasive treatment of GISTs, with special focus on tumor location and, in the treatment of advanced forms, on the possible role of laparoscopy in association with imatinib mesylate therapy.

Methods

The MEDLINE® and Embase® databases were searched for potentially eligible English-language studies published through June 30, 2015. Search terms were "laparoscopy", "laparoscopic", "laparoscopic treatment", "minimally invasive", "minimally invasive treatment", "surgery", "gastrointestinal stromal tumor", "GIST", "gastric", "stomach", "small bowel", "jejunum", "ileum", "bowel", "large intestine", "colon", "rectum", "colorectal", "intra-abdominal", "retroperitoneal", "retroperitoneum", "mesenteric", "mesentery", "omental", and "omentum". The search was limited to English-language original research articles, guidelines, or consensus papers. The reference lists of articles identified were manually searched to locate other articles of relevance.

General considerations for laparoscopic treatment of gists

Once the diagnosis of GIST has been established, the goal of surgery is complete resection while avoiding tumor rupture and achieving negative margins. The 2004 European Society for Medical Oncology (ESMO) Consensus Conference on GISTs recommended that, because of the higher risk of tumor rupture and subsequent peritoneal seeding, laparoscopic surgery should be avoided, but that laparoscopic resection might be acceptable in cases of small (< 2 cm) intramural tumors [17]. The 2007 National Comprehensive Cancer Network (NCCN) Guidelines® emphasized the expanding role of laparoscopy and its safety when performed by experienced surgeons [18]. Whereas the NCCN and ESMO guidelines indicate that nodules ≥ 2 cm in size should be excised and biopsied, some authors recommend excision even of micro-GISTs because of their potential for malignancy [11,19-22]. ESMO recommends resection of smaller nodules located in the esophagus, stomach, and duodenum that are increasing in size, and of rectal nodules of any size. ESMO guidelines recommend that

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laparoscopic excision follow the principles of oncologic surgery and clearly discourage a laparoscopic approach in larger tumors because of the higher risk of tumor rupture and peritoneal relapse [12].

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 [13,23-25]. Nevertheless, because the advantages of laparoscopic surgery are limited to short-term outcomes, its adoption is not justified if essential oncologic principles are not respected. Tumor rupture from intraoperative manipulation leads to an extremely high risk of peritoneal seeding and transforms GISTs of any size into metastatic GISTs. 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 [12].

Conversely, because lymph node involvement is rarely observed, major resection with extended lymphadenectomy should be avoided unless absolutely necessary [11,12]. R0 resection with clear margins of 1–2 cm is adequate to ensure complete surgical resection [26,27]; however, a microscopically involved (R1) margin, rather than a major resection, should be considered in selected cases (e.g., low-risk tumors near the esophagogastric junction, lower rectum, or duodenum) [12,28]. In this setting, as in larger tumors, neoadjuvant TKI therapy can facilitate radical surgery with preservation of organ function, [29-31].

Gastric gists

Most reports of laparoscopic GIST resections involve tumors located in the stomach. As submucosal and lymphatic spread is rarely observed in gastric GISTs, these tumors are often treated by local or wedge resection [32]. In several retrospective series comparing laparoscopic and open approaches, the laparoscopic approach was found to be associated with better short-term and comparable long-term outcomes than those of open surgery [13,33-36]. However, the technical feasibility of treating larger tumors laparoscopically remains questionable; because of the paucity and short follow-up periods of published cohorts, the assumption of higher risk of tumor rupture and peritoneal seeding has not been completely ruled out [24]. Results of studies reporting on laparoscopic resection for gastric gastrointestinal stromal tumors are summarized in (Table 1).

GISTs of the stomach have a better prognosis than GISTs at other sites. In a recent observational cohort study based on published population-based series of operable GISTs in patients who did not receive TKI therapy, GISTs of the stomach were reported to have recurrence-free 20-year survival of about 80% [4]. The estimated risk of recurrence for a tumor with no rupture, a diameter of ≤ 5 cm, and a mitotic count of ≤ 10 high-power fields (HPFs) ranged between 20% and 40%. Conversely, for tumors with the same characteristics but with rupture, the recurrence risk rose to 80% [4].

The median tumor size of gastric GISTs treated laparoscopically is approximately 4 cm, although tumors ranging from 1 cm to 15 cm were included in the cohorts [36,37]. The majority of tumors of the anterior abdominal wall, greater curvature, and fundus are treated with wedge resection using a linear stapler or resection and suturing. Major gastric resections are seldom performed and are usually reserved for tumors of the esophagogastric junction (EGJ) or pyloric area [47,48] (Table 1).

Resection by endoscopic submucosal dissection (ESD) has been demonstrated to be technically feasible for small endophytic lesions in Eastern as well as a few Western centers [49-51], but some issues regarding ESD remain. First, the application of ESD in centers in Europe and the United States is quite limited, and its use in tumors developing from the muscularis propria confers a higher risk of complications such as hemorrhage, perforation, and resection failure [22,32]. Second, few studies have evaluated the suitability and safety of ESD for the treatment of GISTs. In particular, ESD allows enucleation of the tumor with close resection margins. Although gastric GISTs less than 2 cm in diameter are at low risk of recurrence, they should be considered potentially malignant lesions until demonstrated otherwise. Third, the follow-up periods of studies published to date are too short to consider ESD more than investigational [52].

Author (Country)	Accrual period (Study size) [c]	No. (%) of lap. cases	Tumor size [d]	Type of resection [f]	% of conversions	Morbidity (Mortality)	Hospital stay [d]	Overall rec (Local rec)
Otani et al. (Japan) [37]	'93-'04 (60)	38 (63)	NA	WR	0	NA	7.2	NA
Nishimura et al. (Japan) [38]	'93-'04 (67)	39 (58)	3.8	WR/ IGWR	2.6	NA (0)	NA	2.6 (2.6)
Nakamori et al. (Japan) [39]	'98-'03 (56)	25 (44)	NA	WR/ IGWR	0	0 (0)	NA	8 (0)
Karakousis et al. (United States) [34]	'98-'09 (155)	40 (26)	3.6	WR	32.5	15 (0)	4	2.5 (2.5)
De Vogelaere et al. (Belgium) [36]	'97-'10 (31)	31 (100)	4.4	WR	0	3.2 (3.2)	8.5	0
Lee et al. (Korea) [40]	'08-'10 (57)	57 (100)	2.8	WR/ TGWR	0	17.5 (0)	4.7	NA
Melstrom et al. (United States) [13]	'99-'08 (46)	17 (37)	4.3	WR	5.8	11.8 (0)	2.7	0
Valle et al. (Italy) [41]	'04-'12 (38)	38 (100)	3.6	WR/ TGWR/ Gastr.	0	0 (0)	<8	NA
Honda et al. (Japan) [42]	'05-'12 (78)	78 (100)	3.4	WR/ Gastr.[g]	1.3	9 (0)	3	1.3 (1.3)
Lin et al. (China) [25]	'07-'12 (140)	23 (16)	7.2 [e]	WR/ Gastr.	4.3	8.7 (0)	7.2	8.7 (NA)
Masoni et al. (Italy) [43]	'07-'11 (24)	24 (100)	5.5	WR	0	33.3 (0)	3	0
Hsiao et al. (Taiwan) [44]	'02-'12 (39)	18 (46)	6.3	WR	0	0 (0)	8.4	5.5 (0)
Cai et al. (China) [45]	'06-'13 (177)	90 (51)	3.5	WR	NA	4.4 (0)	6.0	1.1 (0)
Goh et al. (Singapore) [46]	'98-'13 (114)	50 (44)	3.5	WR	10	6 (0)	4	0

[a] Data reported refer to laparoscopic cases only.
[b] All studies were retrospective reviews of patient cohorts.
[c] Study size refers to the total number of gastrointestinal stromal tumor cases treated during the study period.
[d] Numbers with decimals are means; whole numbers represent medians.
[e] Tumors less than 5 cm in diameter were excluded from analysis.
[f] WR: wedge resection; IGWR: intragastric wedge resection; TGWR: transgastric wedge resection; Gastr.: distal, proximal, or total gastrectomy with any kind of reconstruction.
[g] Cases of laparoscopic and endoscopic cooperative surgery (LECS) were included in this series.

Table 1: Main characteristics and results of studies reporting on laparoscopic resection for gastric gastrointestinal stromal tumors.

Several hybrid laparoscopic and endoscopic procedures have been described in the setting of minimally invasive treatment of gastric GISTs. Endoscopically assisted laparoscopic resection is the most frequently employed method [35,53]. Interestingly, some Japanese authors proposed endoscopic resection via full-thickness ESD with laparoscopic assistance [54,55]. Laparoscopic and endoscopic cooperative surgery (LECS), as described by Hiki et al., has been utilized for intraluminal protruding lesions, and the authors contemplated the use of ESD to mark the lesion and perform a full-thickness resection of three-fourths of the lesion, completing the resection and suturing the defect laparoscopically. Honda et al. recently reported on LECS technique in 40 patients. The cohort was analyzed together with 38 patients treated with laparoscopic wedge resection (32 cases) or laparoscopic gastrectomy (six patients). The number of complications in the overall series was low (9%), no positive resection margins were demonstrated, and conversion to open surgery was necessary in only one case [42].

Another attractive hybrid procedure that allows treatment of lesions of the posterior gastric wall or EGJ is transgastric laparoscopic resection. Several authors proposed a transgastric approach for laparoscopic resection of lesions of the posterior wall through an anterior gastrotomy performed under endoscopic guidance [35,49,53,56,57]. Others proposed laparoscopic resection via a transgastric approach by positioning trocars through the gastric wall. For this reason, the procedure might be more accurately identified as intragastric laparoscopic resection. It should be performed under endoscopic guidance using two transgastric ports (for smaller lesions) [58] or a laparoscopic camera with an additional trocar [59-62]. Although published reports are still limited, the option of intragastric laparoscopic resection is extremely attractive and presents several theoretical advantages over ESD and the transgastric approach. The intragastric procedure is easier, less time consuming, more reproducible and enables safer resection margins than ESD. It is also less likely than the transgastric approach to transform endoluminal neoplastic disease into extraluminal disease, with less risk of peritoneal seeding as well as less chance of contamination of the peritoneal cavity.

Gist of the small bowel

One-third of GISTs are located in the small bowel [4]. In the pre-imatinib mesylate era, long-term survival associated with small-bowel GISTs was about 50%, which is much lower than that of gastric GISTs [4,63-65].

Few studies have analyzed the results of laparoscopic treatment of small-bowel GISTs in a limited number of patients and are summarized in (Table 2). Nguyen et al. presented a series of 43 patients who underwent laparoscopic treatment for GIST; among these, the tumor was located in the small bowel in 15 cases. Laparoscopic treatment was demonstrated to be feasible even in larger tumors (8.5 cm), but no long-term results were reported [66]. Chen et al. compared 58 patients who underwent laparoscopic (16 cases) and open (42 cases) resection for GIST. Among the 16 patients treated laparoscopically, 7 had a GIST of the jejunum or ileum and underwent laparoscopy-assisted small-bowel resection through a mini laparotomy. No major complications occurred, and the authors concluded that laparoscopic treatment of small-bowel GISTs was feasible and safe and had some advantages in short-term outcome [47]. Liao et al. [68] compared 85 patients who underwent laparoscopic (26 cases) and open (59 cases) resection for GIST of the small bowel. In the laparoscopic group, the tumor was located in the jejunum in 19 patients and in the ileum in 7 patients. The resection was performed laparoscopically and the specimen removed using double protection (endobag and wound protector). The anastomosis was performed intracorporeally with a linear stapler or extracorporeally by hand sewing. The authors confirmed the safety of laparoscopic resection and better short-term results with regard to hospital stay, mean time to oral intake, and duration of analgesia. These experiences confirm the feasibility of laparoscopic treatment of small bowel GISTs, but particular attention should be paid to manipulation of the tumor in order to avoid its rupture and dissemination. The use of plastic bags for tumor retrieval and the application of wound protector in laparoscopy-assisted resections are strongly recommended.

Gist of the colon and rectum

Few data are available on colorectal GISTs, which represent 0.1% of all tumors of the colon and rectum and occur more frequently in the rectum than in the colon [69-71]. As with small-bowel GISTs, 10-year disease-free survival is nearly 50%, but the recurrence risk, unlike that of small-bowel GISTs, does not decrease over time [4].

Typically, symptomatic colonic GISTs present as large transmural tumors with frequent intraluminal and outwardly protruding components [69]. Although definite data on colonic GISTs are lacking, laparoscopic resection could represent an option for tumors able to be approached laparoscopically with strict adherence to oncologic principles [72].

Even rectal GISTs usually present as large masses frequently adherent to the pelvic floor or adjacent organs. In this setting, complete tumor resection often requires extended procedures with sacrifice of adjacent organs and the anal sphincter. In the pre-imatinib mesylate era, though mutilating, extended procedures were performed, residual disease reportedly occurred in 30% of cases and recurrence rates exceeded 40% [73-76].

In a recent study, Wilkinson et al. reported on 19 patients with primary rectal GIST treated over a 12-year period. Neoadjuvant imatinib was used in 15 patients, significantly reducing mean tumor size and mitotic count and enabling sphincter-sparing surgery in 7 out of 9 patients who underwent resection. The authors concluded that the

Author (Country)	Accrual period (Study size) [c]	No. of small bowel cases	Tumor size [d]	Type of resection	% of conversions	Morbidity (Mortality)	Hospital stay [d]	Overall rec (Local rec) [d]
Nguyen et al. (United States) [66]	'00-'05 (43)	15	3.7	Lap./ Lap. ass	13	6.7 (0)	4	NA
Chen et al. (Taiwan) [47]	'05-'10 (16)	7	NA	Lap. ass	6	NA (0)	NA	14.3 (0)
Sakra et al. (Czech Republic) [67]	'07-'10 (13)	2	NA	Lap.	50	NA (0)	NA	NA (0)
Liao et al. (Taiwan) [68]	'05-'13 (26)	26	4.2	Lap./Lap. ass	7.7	3.8 (0)	8	15.4 (NA)

[a] Data reported refer to laparoscopic cases only.
[b] All studies were retrospective reviews of patient cohorts.
[c] Study size refers to the total number of gastrointestinal stromal tumor cases treated by laparoscopy during the study period.
[d] Numbers with decimals are means; whole numbers represent medians.

Table 2: Main characteristics and results of studies reporting on laparoscopic resection for gastrointestinal stromal tumor of the small bowel.

use of neoadjuvant imatinib mesylate therapy for rectal GIST decreased both tumor size and mitotic count, which allowed more sphincter-sparing surgeries [77].

For rectal GIST, achieving a potentially curative (R0) resection seems to be the major determinant of local relapse and long-term survival. Although adherence to total mesorectal excision principles is not strictly required because of the rarity of lymph node involvement, tearing of the tumor capsule frequently occurs and has been demonstrated to be a major determinant of recurrence. Interestingly, recurrence is described to be locoregional in transanal local resections and peritoneal in transabdominal rectal resections [73,76].

In the guidelines of Miettinen et al., which are based on the analysis of 111 rectal GISTs ≤ 2 cm in size with a mitotic index of ≤ 5 per 50 HPFs are considered benign, while the risk of recurrence increases for larger tumors or tumors with a mitotic index < 5 [69]. On this basis, transanal or transvaginal local resection is proposed for smaller tumors, and rectal resection with or without conservation of the anal sphincter is proposed for larger tumors [74,78]. In the pre-imatinib mesylate era, tumors within 5 cm from the anal verge were frequently treated with abdominoperineal resection.

Actually, the use of both neoadjuvant TKI therapy and laparoscopy radically changed the approach to the disease. Results of studies reporting on laparoscopic resection for rectal gastrointestinal stromal tumors are summarized in (Table 3). Fujimoto et al. described five cases of GIST of the lower rectum (within 5 cm from the anal verge) treated by neoadjuvant TKI therapy and laparoscopic partial or complete intersphincteric resection. R0 resection was achieved in all patients and no recurrences were observed after a mean follow-up period of 31 months [31]. Similarly, laparoscopic sphincter-sparing surgery has been demonstrated to be feasible by other authors [79,80-82]. Chang et al. recently described the case of a 5-cm GIST of the lower rectum treated by laparoscopic-assisted excision. After the middle and lower rectum was mobilized, the tumor was excised and the specimen extracted from the anus, and the defect was sutured transanally [80].

Extra-intestinal gist

Extra-intestinal GISTs (e-GISTs) usually present as large masses of the omentum, mesentery, and retroperitoneal space. To our knowledge, no report of laparoscopic treatment of an e-GIST has been published to date. Laparoscopy is not usually considered for e-GISTs, even if it is theoretically feasible, because of their size and uncertain diagnosis at preoperative staging.

Tki and laparoscopic treatment

TKI therapy is widely accepted as the standard treatment for patients with metastatic and/or non-resectable GISTs [11,20,83]. Indeed, several reports have demonstrated the efficacy of imatinib mesylate in the neoadjuvant setting in cases of primary as well as recurrent or metastatic non-resectable GIST [84,85]. Current NCCN and ESMO guidelines recommend neoadjuvant therapy for patients with large tumors, where resection would cause undue morbidity or functional deficit, and small tumors in difficult-to-treat areas such as the EGJ or low rectum [11,12]. Response is seen in more than 80% of cases, with a response plateau generally reached after 6–12 months of therapy. Serial computed tomography (CT) scanning performed at 2- to 3-month intervals is the preferred method for evaluating response and for decision-making regarding surgical resection [15,16,32,84].

The adoption of laparoscopy in such cases is not yet supported by the literature. However, several small case series have described the use of neoadjuvant imatinib mesylate therapy in low rectal GISTs in order to reduce recurrence and accomplish sphincter-sparing surgery [31,81,82]. Neoadjuvant imatinib therapy has also been reported for GISTs located at the EGJ [86].

In cases of metastatic GIST with good response, surgical resection should be considered when R0 resection is possible, with the aim of avoiding imatinib mesylate resistance with subsequent progression. Similarly, in cases of limited progression, surgery plays an important role in improving survival as well as quality of life. Furthermore, surgical resection is indicated in metastatic disease to treat tumor-related complications. Although not yet proven, laparoscopy may, when technically feasible and safe, play a role in minimizing surgical stress and postoperative immunosuppression as well as in allowing a short interruption of imatinib mesylate therapy (Figure 1A-C).

Conclusions

Laparoscopic surgery is frequently used to treat GISTs. Whereas many studies have reported on the feasibility and safety of laparoscopic treatment of gastric GISTs, fewer data are available for small-bowel and colorectal GISTs. Most gastric GISTs are suitable for laparoscopic wedge resection, while gastric GISTs in difficult-to-treat areas may benefit from innovative approaches such as transgastric and intragastric resections. Primary resection of large rectal GISTs carries a high risk of recurrence. In this setting, as in other difficult-to-treat areas, neoadjuvant imatinib therapy should be considered to improve long-term results and reduce surgical trauma. In selected cases, the combination of imatinib mesylate therapy and laparoscopy can minimize surgical trauma. Similarly, laparoscopic treatment in advanced and metastatic cases with very good responses to TKI therapy should, in principle, not be avoided.

Author (Country)	Type of study (Accrual period)	No. of cases	Tumor size [a]	Mitotic count [a]	Neoadjuvant imatimib [b]	Type of resection	% of conversions	Morbidity (Mortality)	Hospital stay [c]	Overall rec (Local rec)
Ebihara et al. (Japan) [79]	Case report	1	80	5/50	8	Lap. ISR	no	no	NA	no
Chang et al. (Japan) [80]	Case report	1	50	0/50	no	Lap. resection with transanal suture	no	no	NA	no
Nakamura et al. (Japan) [81]	Case report	1	80	<5/50	12	Lap. assisted transanal resection	no	NA	NA	no
Fujimoto et al. (Japan) [31]	Retrosp. ('08-'11)	5	31	NA	8.6	Lap. ISR	0	ileus (0)	16	0

[a] Tumor diameter and mitotic count (50 per high-power field) are before neoadjuvant imatimib treatment.
[b] Weeks of neoadjuvant imatimib treatment.
[c] Numbers with decimals are means; whole numbers represent medians.

Table 3: Main characteristics and results of studies on laparoscopic resection for rectal gastrointestinal stromal tumors.

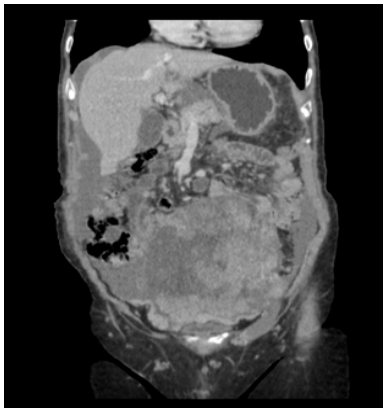

Figure 1A: Symptomatic abdominopelvic mass, 180 ×170 mm, with diffuse peritoneal carcinomatosis and ultrasound-guided biopsy confirming GIST.

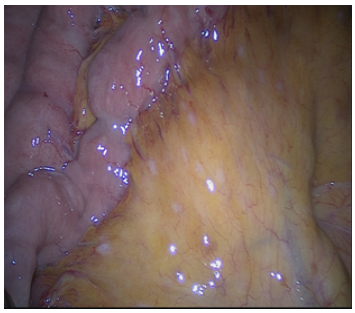

Figure 1B: Laparoscopic view in course of laparoscopic-assisted ileal resection with biopsy-proven complete response of the peritoneum after neoadjuvant imatinib therapy (400 mg daily for 12 weeks).

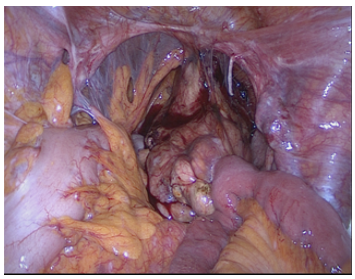

Figure 1C: Laparoscopic view in course of laparoscopic-assisted ileal resection with biopsy-proven complete response of the peritoneum after neoadjuvant imatinib therapy (400 mg daily for 12 weeks).

References

1. Rossi CR, Mocellin S, Mencarelli R, Foletto M, Pilati P, et al. (2003) Gastrointestinal stromal tumors: from a surgical to a molecular approach. Int J Cancer 107: 171-176.
2. Fletcher CD, Berman JJ, Corless C, Gorstein F, Lasota J, et al. (2002) Diagnosis of gastrointestinal stromal tumors: A consensus approach. Hum Pathol 33: 459-465.
3. Miettinen M, Lasota J (2006) Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. Arch Pathol Lab Med 130: 1466-1478.
4. Joensuu H, Vehtari A, Riihimäki J, Nishida T, Steigen SE, et al. (2012) Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts. Lancet Oncol 13: 265-274.
5. Kawanowa K, Sakuma Y, Sakurai S, Hishima T, Iwasaki Y, et al. (2006) High incidence of microscopic gastrointestinal stromal tumors in the stomach. Hum Pathol 37: 1527-1535.
6. Agaimy A, Wünsch PH, Hofstaedter F, Blaszyk H, Rümmele P, et al. (2007) Minute gastric sclerosing stromal tumors (GIST tumorlets) are common in adults and frequently show c-KIT mutations. Am J Surg Pathol 31: 113-120.
7. Dematteo RP, Ballman KV, Antonescu CR, Maki RG, Pisters PW, et al. (2009) Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. Lancet 373: 1097-1104.
8. Blanke CD, Demetri GD, von Mehren M, Heinrich MC, Eisenberg B, et al. (2008) Long-term results from a randomized phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. J Clin Oncol 26: 620-625.
9. Gold JS, Gönen M, Gutiérrez A, Broto JM, García-del-Muro X, et al. (2009) Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localised primary gastrointestinal stromal tumour: a retrospective analysis. Lancet Oncol 10: 1045-1052.
10. Kindblom LG, Remotti HE, Aldenborg F, Meis-Kindblom JM (1998) Gastrointestinal pacemaker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. Am J Pathol 152: 1259-1269.
11. Demetri GD, von Mehren M, Antonescu CR, DeMatteo RP, Ganjoo KN, et al. (2010) NCCN Task Force report: update on the management of patients with gastrointestinal stromal tumors. J Natl Compr Canc Netw 8 Suppl 2: S1-41.
12. European Sarcoma Network Working Group (2012) Gastrointestinal stromal tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 7: 49-55.
13. Melstrom LG, Phillips JD, Bentrem DJ, Wayne JD (2012) Laparoscopic versus open resection of gastric gastrointestinal stromal tumors. Am J Clin Oncol 35: 451-454.
14. De Vogelaere K, Hoorens A, Haentjens P, Delvaux G (2013) Laparoscopic versus open resection of gastrointestinal stromal tumors of the stomach. Surg Endosc 27: 1546-1554.
15. Hohenberger P, Eisenberg B (2010) Role of surgery combined with kinase inhibition in the management of gastrointestinal stromal tumor (GIST). Ann Surg Oncol 17: 2585-2600.
16. Yang W, Yu J, Gao Y, Shen Q, Zhang Q, et al. (2014) Preoperative imatinib facilitates complete resection of locally advanced primary GIST by a less invasive procedure. Med Oncol 31: 133.
17. Blay JY, Bonvalot S, Casali P, Choi H, Debiec-Richter M, et al. (2004) Consensus meeting for the management of gastrointestinal stromal tumors. Report of the GIST Consensus Conference of 20-21 March 2004, under the auspices of ESMO. Ann Oncol 16: 566-578.
18. Demetri GD, Benjamin RS, Blanke CD, Blay JY, Casali P, et al. (2007) NCCN Task Force report: management of patients with gastrointestinal stromal tumor (GIST)--update of the NCCN clinical practice guidelines. J Natl Compr Canc Netw 5 Suppl 2: S1-29.
19. Blackstein ME, Blay JY, Corless C, Driman DK, Riddell R, et al. (2006) Gastrointestinal stromal tumours: consensus statement on diagnosis and treatment. Can J Gastroenterol 20: 157-163.
20. Casali PG, Jost L, Reichardt P, Schlemmer M, Blay JY (2009) ESMO Guidelines Working Group, Gastrointestinal stromal tumours: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 4: 64-67.
21. Mussi C, Ronellenfitsch U, Jakob J, Tamborini E, Reichardt P, et al. (2010) Post-imatinib surgery in advanced/metastatic GIST: is it worthwhile in all patients? Ann Oncol 21: 403-408.
22. Jeong IH, Kim JH, Lee SR, Kim JH, Hwang JC, et al. (2012) Minimally invasive treatment of gastric gastrointestinal stromal tumors: laparoscopic and endoscopic approach. Surg Laparosc Endosc Percutan Tech 22: 244-250.
23. Koh YX, Chok AY, Zheng HL, Tan CS, Chow PK, et al. (2013) A systematic review and meta-analysis comparing laparoscopic versus open gastric resections for gastrointestinal stromal tumors of the stomach. Ann Surg Oncol 20: 3549-3560.
24. Liang JW, Zheng ZC, Zhang JJ, Zhang T, Ke Chen, et al. (2013) Laparoscopic

versus open gastric resections for gastric gastrointestinal stromal tumors: a meta-analysis. Surg Laparosc Endosc Percutan Tech 23: 378-387.

25. Lin J, Huang C, Zheng C, Li P, Xie J, et al. (2014) Laparoscopic versus open gastric resection for larger than 5 cm primary gastric gastrointestinal stromal tumors (GIST): a size-matched comparison. Surg Endosc 28: 2577-2583.

26. Novitsky YW, Kercher KW, Sing RF, Heniford BT (2006) Long-term outcomes of laparoscopic resection of gastric gastrointestinal stromal tumors. Ann Surg 243: 738-745.

27. Iwahashi M, Takifuji K, Ojima T, Nakamura M, Nakamori M, et al. (2006) Surgical management of small gastrointestinal stromal tumors of the stomach. World J Surg 30: 28-35.

28. DeMatteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM, et al. (2000) Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. Ann Surg 231: 51-58.

29. Eisenberg BL, Harris J, Blanke CD, Demetri GD, Heinrich MC, et al. (2009) Phase II trial of neoadjuvant/adjuvant imatinib mesylate (IM) for advanced primary and metastatic/recurrent operable gastrointestinal stromal tumor (GIST): early results of RTOG 0132/ACRIN 6665. J Surg Oncol 99: 42-47.

30. Fiore M, Palassini E, Fumagalli E, Pilotti S, Tamborini E, et al. (2009) Preoperative imatinib mesylate for unresectable or locally advanced primary gastrointestinal stromal tumors (GIST). Eur J Surg Oncol 35: 739-745.

31. Fujimoto Y, Akiyoshi T, Konishi T, Nagayama S, Fukunaga Y, et al. (2014) Laparoscopic sphincter-preserving surgery (intersphincteric resection) after neoadjuvant imatinib treatment for gastrointestinal stromal tumor (GIST) of the rectum. Int J Colorectal Dis 29: 111-116.

32. Mullady DK, Tan BR (2013) A multidisciplinary approach to the diagnosis and treatment of gastrointestinal stromal tumor. J Clin Gastroenterol 47: 578-585.

33. Goh BK, Chow PK, Chok AY, Chan WH, Chung YF, et al. (2010) Impact of the introduction of laparoscopic wedge resection as a surgical option for suspected small/medium-sized gastrointestinal stromal tumors of the stomach on perioperative and oncologic outcomes. World J Surg 34: 1847-1852.

34. Karakousis GC, Singer S, Zheng J, Gonen M, Coit D, et al. (2011) Laparoscopic versus open gastric resections for primary gastrointestinal stromal tumors (GISTs): a size-matched comparison. Ann Surg Oncol 18: 1599-1605.

35. Kiyozaki H, Saito M, Chiba H, Takata O, Rikiyama T (2014) Laparoscopic wedge resection of the stomach for gastrointestinal stromal tumor (GIST): non-touch lesion lifting method. Gastric Cancer 17: 337-340.

36. De Vogelaere K, Van Loo I, Peters O, Hoorens A, Haentjens P, et al. (2012) Laparoscopic resection of gastric gastrointestinal stromal tumors (GIST) is safe and effective, irrespective of tumor size. Surg Endosc 26: 2339-2345.

37. Otani Y, Furukawa T, Yoshida M, Saikawa Y, Wada N, et al. (2006) Operative indications for relatively small (2-5 cm) gastrointestinal stromal tumor of the stomach based on analysis of 60 operated cases. Surgery 139: 484-492.

38. Nishimura J, Nakajima K, Omori T, Takahashi T, Nishitani A, et al. (2007) Surgical strategy for gastric gastrointestinal stromal tumors: laparoscopic vs. open resection. Surg Endosc 21: 875-878.

39. Nakamori M, Iwahashi M, Nakamura M, Tabuse K, Mori K, et al. (2008) Laparoscopic resection for gastrointestinal stromal tumors of the stomach. Am J Surg 196: 425-429.

40. Lee CH, Hyun MH, Kwon YJ, Cho SI, Park SS (2012) Deciding laparoscopic approaches for wedge resection in gastric submucosal tumors: a suggestive flow chart using three major determinants. J Am Coll Surg 215: 831-840.

41. Valle M, Federici O, Carboni F, Carpano S, Benedetti M (2014) Gastrointestinal stromal tumors of the stomach: the role of laparoscopic resection. Single-centre experience of 38 cases. Surg Endosc 28: 1040-1047.

42. Honda M, Hiki N, Nunobe S, Ohashi M, Kiyokawa T, et al. (2014) Long-term and surgical outcomes of laparoscopic surgery for gastric gastrointestinal stromal tumors. Surg Endosc 28: 2317-2322.

43. Masoni L, Gentili I, Maglio R, Meucci M, D'Ambra G, et al. (2014) Laparoscopic resection of large gastric GISTs: feasibility and long-term results. Surg Endosc 28: 2905-2910.

44. Hsiao CY, Yang CY, Lai IR, Chen CN, Lin MT (2015) Laparoscopic resection for large gastric gastrointestinal stromal tumor (GIST): intermediate follow-up results. Surg Endosc 29: 868-873.

45. Cai JQ, Chen K, Mou YP, Pan Y, Xu XW, et al. (2015) Laparoscopic versus open wedge resection for gastrointestinal stromal tumors of the stomach: a single-center 8-year retrospective cohort study of 156 patients with long-term follow-up. BMC Surg 15: 58.

46. Goh BK, Goh YC, Eng AK, Chan WH, Chow PK, et al. (2015) Outcome after laparoscopic versus open wedge resection for suspected gastric gastrointestinal stromal tumors: A matched-pair case-control study. Eur J Surg Oncol 41: 905-910.

47. Chen YH, Liu KH, Yeh CN, Hsu JT, Liu YY, et al. (2012) Laparoscopic resection of gastrointestinal stromal tumors: safe, efficient, and comparable oncologic outcomes. J Laparoendosc Adv Surg Tech A 22: 758-763.

48. Ohtani H, Maeda K, Noda E, Nagahara H, Shibutani M, et al. (2013) Meta-analysis of laparoscopic and open surgery for gastric gastrointestinal stromal tumor. Anticancer Res 33: 5031-5041.

49. Lee IL, Lin PY, Tung SY, Shen CH, Wei KL, et al. (2006) Endoscopic submucosal dissection for the treatment of intraluminal gastric subepithelial tumors originating from the muscularis propria layer. Endoscopy 38: 1024-1028.

50. Hwang JC, Kim JH, Kim JH, Shin SJ, Cheong JY, et al. (2009) Endoscopic resection for the treatment of gastric subepithelial tumors originated from the muscularis propria layer. Hepatogastroenterology 56: 1281-1286.

51. Catalano F, Rodella L, Lombardo F, Silano M, Tomezzoli A, et al. (2013) Endoscopic submucosal dissection in the treatment of gastric submucosal tumors: results from a retrospective cohort study. Gastric Cancer 16: 563-570.

52. Abe N, Takeuchi H, Ooki A, Nagao G, Masaki T, et al. (2013) Recent developments in gastric endoscopic submucosal dissection: towards the era of endoscopic resection of layers deeper than the submucosa. Dig Endosc 1: 64-70.

53. Wilhelm D, von Delius S, Burian M, Schneider A, Frimberger E, et al. (2008) Simultaneous use of laparoscopy and endoscopy for minimally invasive resection of gastric subepithelial masses - analysis of 93 interventions. World J Surg 32: 1021-1028.

54. Hiki N, Yamamoto Y, Fukunaga T, Yamaguchi T, Nunobe S, et al. (2008) Laparoscopic and endoscopic cooperative surgery for gastrointestinal stromal tumor dissection. Surg Endosc 22: 1729-1735.

55. Abe N, Takeuchi H, Yanagida O, Masaki T, Mori T, et al. (2009) Endoscopic full-thickness resection with laparoscopic assistance as hybrid NOTES for gastric submucosal tumor. Surg Endosc 23: 1908-1913.

56. Sakamoto Y, Sakaguchi Y, Akimoto H, Chinen Y, Kojo M, et al. (2012) Safe laparoscopic resection of a gastric gastrointestinal stromal tumor close to the esophagogastric junction. Surg Today 42: 708-711.

57. Xu X, Chen K, Zhou W, Zhang R, Wang J, et al. (2013) Laparoscopic transgastric resection of gastric submucosal tumors located near the esophagogastric junction. J Gastrointest Surg 17: 1570-1575.

58. Vecchio R, Marchese S, Amore FF, La Corte F, Ferla F, et al. (2013) Laparoscopic-endoscopic rendez-vous resection of iuxta-cardial gastric GIST. G Chir 34: 145-148.

59. Taniguchi E, Kamiike W, Yamanishi H, Ito T, Nezu R, et al. (1997) Laparoscopic intragastric surgery for gastric leiomyoma. Surg Endosc 11: 287-289.

60. Li VK, Hung WK, Chung CK, Ying MW, Lam BY, et al. (2008) Laparoscopic intragastric approach for stromal tumours located at the posterior gastric wall. Asian J Surg 31: 6-10.

61. Conrad C, Nedelcu M, Ogiso S, Aloia TA, Vauthey JN, et al. (2015) Techniques of intragastric laparoscopic surgery. Surg Endosc 29: 202-206.

62. Pedrazzani C, Vitali M, Guglielmi A (2015) A Case of Unexpected Gastric Mass. JAMA Surg 150: 1187-1188.

63. Wu TJ, Lee LY, Yeh CN, Wu PY, Chao TC, et al. (2006) Surgical treatment and prognostic analysis for gastrointestinal stromal tumors (GISTs) of the small intestine: before the era of imatinib mesylate. BMC Gastroenterol 6: 29.

64. Chiang NJ, Chen LT, Tsai CR, Chang JS (2014) The epidemiology of gastrointestinal stromal tumors in Taiwan, 1998-2008: a nation-wide cancer registry-based study. BMC Cancer 14: 102.

65. Corless CL, Ballman KV, Antonescu CR, Kolesnikova V, Maki RG, et al. (2014) Pathologic and molecular features correlate with long-term outcome after

adjuvant therapy of resected primary GI stromal tumor: the ACOSOG Z9001 trial. J Clin Oncol 32: 1563-1570.

66. Nguyen SQ, Divino CM, Wang JL, Dikman SH (2006) Laparoscopic management of gastrointestinal stromal tumors. Surg Endosc 20: 713-716.

67. Sákra L, Siller J, Vyhnálek P, Hácová M (2011) Surgical treatment of gastric and small bowel gastrointestinal stromal tumours. Wideochir Inne Tech Maloinwazyjne 6: 138-143.

68. Liao CH, Yeh CN, Wang SY, Fu CY, Tsai CY, et al. (2015) Surgical option for intestinal gastrointestinal stromal tumors--perioperative and oncological outcomes of laparoscopic surgery. Anticancer Res 35: 1033-1040.

69. Miettinen M, Sarlomo-Rikala M, Sobin LH, Lasota J (2000) Gastrointestinal stromal tumors and leiomyosarcomas in the colon: a clinicopathologic, immunohistochemical, and molecular genetic study of 44 cases. Am J Surg Pathol 24: 1339-1352.

70. Miettinen M, Furlong M, Sarlomo-Rikala M, Burke A, Sobin LH, et al. (2001) Gastrointestinal stromal tumors, intramural leiomyomas, and leiomyosarcomas in the rectum and anus: a clinicopathologic, immunohistochemical, and molecular genetic study of 144 cases. Am J Surg Pathol 25: 1121-1133.

71. Niazi AK, Kaley K, Saif MW (2014) Gastrointestinal stromal tumor of colon: a case report and review of literature. Anticancer Res 34: 2547-2550.

72. Theodoropoulos DG (2011) Gastrointestinal tumors of the colon and rectum. Clin Colon Rectal Surg 24: 161-170.

73. Tielen R, Verhoef C, van Coevorden F, Reyners AK, van der Graaf WT, et al. (2013) Surgical management of rectal gastrointestinal stromal tumors. J Surg Oncol 107: 320-323.

74. Jakob J, Mussi C, Ronellenfitsch U, Wardelmann E, Negri T, et al. (2013) Gastrointestinal stromal tumor of the rectum: results of surgical and multimodality therapy in the era of imatinib. Ann Surg Oncol 20: 586-592.

75. Xiao CC, Zhang S, Wang MH, Huang LY, Wu P, et al. (2013) Clinicopathological features and prognostic factors of rectal gastrointestinal stromal tumors. J Gastrointest Surg 17: 793-798.

76. Agaimy A, Vassos N, Märkl B, Meidenbauer N, Köhler J, et al. (2013) Anorectal gastrointestinal stromal tumors: a retrospective multicenter analysis of 15 cases emphasizing their high local recurrence rate and the need for standardized therapeutic approach. Int J Colorectal Dis 28: 1057-1064.

77. Wilkinson MJ, Fitzgerald JE, Strauss DC, Hayes AJ, Thomas JM, et al. (2015) Surgical treatment of gastrointestinal stromal tumour of the rectum in the era of imatinib. Br J Surg 102: 965-971.

78. Liu H, Yan Z, Liao G, Yin H (2014) Treatment strategy of rectal gastrointestinal stromal tumor (GIST). J Surg Oncol 109: 708-713.

79. Ebihara Y, Okushiba S, Kawarada Y, Kitashiro S, Katoh H, et al. (2008) Neoadjuvant imatinib in a gastrointestinal stromal tumor of the rectum: report of a case. Surg Today 38: 174-177.

80. Chang SC, Ke TW, Chiang HC, Wu C, Chen WT (2010) Laparoscopic excision is an alterative method for rectal gastrointestinal stromal tumor. Surg Laparosc Endosc Percutan Tech 20: 284-287.

81. Nakamura T, Mitomi H, Onozato W, Sato T, Ikeda A, et al. (2012) Laparoscopic resection of a gastrointestinal stromal tumor of the rectum after treatment with imatinib mesylate: report of a case. Surg Today 42: 1096-1099.

82. Wang JP, Wang T, Huang MJ, Wang L, Kang L, et al. (2011) The role of neoadjuvant imatinib mesylate therapy in sphincter-preserving procedures for anorectal gastrointestinal stromal tumor. Am J Clin Oncol 34: 314-316.

83. Rutkowski P, Gronchi A, Hohenberger P, Bonvalot S, Schöffski P, et al. (2013) Neoadjuvant imatinib in locally advanced gastrointestinal stromal tumors (GIST): the EORTC STBSG experience. Ann Surg Oncol 20: 2937-2943.

84. Wang D, Zhang Q, Blanke CD, Demetri GD, Heinrich MC, et al. (2012) Phase II trial of neoadjuvant/adjuvant imatinib mesylate for advanced primary and metastatic/recurrent operable gastrointestinal stromal tumors: long-term follow-up results of Radiation Therapy Oncology Group 0132. Ann Surg Oncol 19: 1074-1080.

85. Bednarski BK, Araujo DM, Yi M, Torres KE, Lazar A, et al. (2014) Analysis of prognostic factors impacting oncologic outcomes after neoadjuvant tyrosine kinase inhibitor therapy for gastrointestinal stromal tumors. Ann Surg Oncol 21: 2499-2505.

86. Cavaliere D, Vagliasindi A, Mura G, Framarini M, Giorgetti G, et al. (2007) Downstaging of a gastric GIST by neoadjuvant imatinib and endoscopic assisted laparoscopic resection. Eur J Surg Oncol 33: 1044-1046.

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