Original Article

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Surgical outcomes of locally advanced gastrointestinal stromal tumors after multivisceral resection: A retrospective study of 64 patients at a single institution

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SUMMARY To analyze the outcome in patients who have undergone multivisceral resection (MVR) for locally advanced gastrointestinal stromal tumors (GISTs), and identify the risk factors for tumor recurrence and postoperative morbidity. Sixty-four patients who operated for locally advanced GISTs with MVR in PPeking University Cancer Hospital Sarcoma Center (PUCHSC) between 2013 and 2021 were identified. Clinicopathologic characteristics, surgical outcomes, recurrence, and 5-year recurrence-free and overall survival were evaluated. The mean age of the patients was 60 years. Mean tumor size was 11.1 cm. Complete resection was achieved in all patients. The estimated 5-year recurrence-free and overall survival were 86.6% and 90.0%, respectively. Independent factor of recurrence following surgery was mitotic count on multivariate analysis. Overall postoperative morbidity was 53.1% (*n* = 34). Severe morbidity was 21.9% (*n* = 14). The most common severe complication was clinically relevant pancreatic fistula (*n* = 12, 18.8%), followed by anastomotic leakage (*n* = 4, 6.3%) and Intraabdominal abscess (*n* = 4, 6.3%). Multivariate analysis showed that preoperative imatinib therapy could reduce overall morbidity. Long operation time, combined colectomy and pancreatectomy were independent risk factors for postoperative severe morbidity. Compared to partial pancreatectomy, pancreaticoduodenectomy (PD) was significantly increased the incidence of severe morbidity. In conclusion, compared to systemic therapy alone, the outcome of locally advanced GISTs after MVR was more favorable. Despite the high overall morbidity, the postoperative severe morbidity and mortality of MVR were acceptable. Preoperative imatinib therapy should be recommended whenever possible. Combined pancreatectomy and colectomy are associated with significant postoperative severe morbidities. PD should be thoroughly discussed and be subject to MDT approach before surgery.

Keywords gastrointestinal stromal tumors; multivisceral resection; postoperative morbidity; pancreatectomy; surgical outcomes

1. Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract, and surgery was the mainstay of curative treatment. Although the majority of GISTs could underwent minimal invasive surgery at presentation, a significant number of GISTs are locally advanced, requiring more challenging and complex operations. In a recent study, 11% of 908 GISTs required multivisceral resection (MVR) to achieve complete resection (*1*).

The long-term outcome of unresectable locally advanced GISTs was extremely poor, with a median overall survival time of 3.9 years and 10-year overall survival rates of 20% (*2*). Although imatinib therapy prior to surgery was recommended by most guidelines, which may play an important role by downsizing the tumor, in this way decreasing the extent of resection, unfortunately the reported response rate was not satisfactory (SD/PD cases ranged from 18.6-83%) (*3-5*). Once downsizing failed, MVR remains the only chance of cure. The reported 5-year OS for locally advanced GISTs after MVR ranged from 66.9-80.2% (*6-8*). However, the risk factors associated with recurrence were not well described.

In addition, the safety of MVR remains controversial. In 2015, a retrospective study was reported by Racz (*6*), who compared the perioperative outcomes of 110 patients who required MVR versus single-organ resection (SOR) for GISTs, and concluded that MVR had more

complications than SOR. However, another study with opposite conclusions was published 2 years later. With a series of 187 GISTs, there was no significant difference in in-hospital morbidity and mortality on comparison of MVR versus SOR groups (*7*).

The aim of the study was to analyze the short and long-term outcome of patients who underwent MVR for locally advanced GISTs and identify the risk factors for tumor recurrence and postoperative morbidity.

2. Materials and Methods

2.1. Patients

The study was carried out under the approval of the Ethics Committee of Peking University Cancer Hospital. All patients gave informed consent according to the procedures required by the Institutional Review Board of Peking University Cancer Hospital and Institute and in accordance with the Declaration of Helsinki. All consecutive patients who operated for GISTs with MVR in Peking University Cancer Hospital Sarcoma Center (PUCHSC) between 2013 and 2021 were retrospectively investigated. Clinicopathological data were reviewed from the medical records. All patients had complete preoperative imaging (thorax, abdomen, and pelvic CT scan or MRI) and an image-guided percutaneous coaxial core needle biopsy. Decisions were made by multi-disciplinary team (MDT), and operations were performed by same surgical group. Histopathological results were systematically confirmed by an expert pathologist in soft tissue sarcomas.

2.2. Postoperative morbidities and follow-up

Postoperative morbidities (POM) were graded according to the seven grades of the Clavien-Dindo classification (I, II, IIIa, IIIb, IVa, IVb, and V), and considered severe in case of grade ≥ 3. Postoperative pancreatic fistulas (POPF) were reported according to the International Study Group for Pancreatic Fistula (ISGPF) score, and grade B and C were considered "severe". The patients were prospectively followed with clinical examination, chest X-ray, and abdominopelvic computed tomography (CT) or magnetic resonance imaging (MRI) every three months for the first two years, every six months for the next three years, and yearly thereafter.

2.3. Statistical analysis

Patient characteristics, operative factors, and type of MVR were compared between patients who did and did not experience severe morbidity. Univariate and multivariate logistic regression analyses were conducted to identify independent risk factors for severe morbidity. Overall survival (OS) was defined as the time from surgery to last follow-up or death. Disease-free survival (DFS)was defined as the time from surgery to recurrence or metastasis, last follow-up or death, whichever occurred first. OS and DFS were estimated by Kaplan–Meier method. Statistical analysis was performed using SPSS 22.0.

3. Results

3.1. Patient characteristics

Sixty-four patients with locally advanced GISTs underwent MVR in our institution between 2013 and 2021. Median age at surgery was 60 years. Twenty-six (41%) patients had received neoadjuvant imatinib therapy. Complete resection was achieved in all patients. The mean tumor size was 11.1 cm, and median number of resected contiguous organ for each patient was 2. The most common resected contiguous organ was pancreas (62.5%), followed by spleen (43.8%) and colon (43.8%). Forty-two (66%) patients received adjuvant imatinib therapy within one month after surgery. Demographic and clinicopathological data are summarized in Table 1. The median follow-up was 55 months.

3.2. Postoperative morbidity

Postoperative overall morbidity was 53.1% (*n* = 34), and severe morbidity was 21.9% (*n* = 14). The most common

Table 1. Demographic and clinico-pathological data

Characteristics	*n* = 64 (100%)
Sex: male/female [ratio]	30/34 [0.88]
Median age, years [range]	60 [29–80]
Tumor site	
Gastric	32 (50)
Small bowel	32 (50)
Preoperative imatinib therapy	26 (41)
Postoperative imatinib therapy	42 (66)
Surgery	
Multiviceral resection (MVR)	64 (100)
Median number of resected contiguous organ [range]	2 [1–6]
Associated resections	
Pancreas	40 (62.5)
Spleen	28 (43.8)
Colon	28 (43.8)
Diaphragm	10 (15.6)
Liver	8 (12.5)
Other (lung, kidney, adrenal gland, uterus, bladder)	16 (25)
Median operative time (min) [range]	325 [130–518]
Median perioperative bleeding (mL) [range]	400 [20–2300]
Pathological finding	
Mean tumor size at resection specimen, cm [range]	11.1 [5–26]
Complete resection	64 (100)
Microscopic organ involvement Mutational status	20 (31.3)
KIT exon 11 mutation	40 (62.5)
KIT exon 9 mutation	14 (21.9)
KIT exon 13 mutation	4 (6.3)
PDGFRA exon 18	4 (6.3)
Wild-type	2 (3.1)

severe complication was clinically relevant pancreatic fistula (n = 12, 18.8%), followed by anastomotic leakage (n = 4, 6.3%) and Intraabdominal deep abscess (n = 4, 6.3%). Most severe complications could be managed by percutaneous drainage successfully, and only two patients (1.6%) required surgical reintervention for acute peritonitis secondary to anastomotic leakage and hemorrhage. Postoperative complications are illustrated in Table 2. Multivariate analysis showed that preoperative imatinib therapy was independent risk factor for overall morbidity. Long operation time, combined colectomy and pancreatectomy were independent risk factors for severe morbidity (Table 3). More patients had received neoadjuvant imatinib in non-morbidity group (53.3% *vs* 29.4%), and patients in severe morbidity group were more likely to have combined pancreatectomy (92.9% *vs* 54%) and colectomy (78.6% *vs* 34.0%,) when compared with patients in non-severe morbidity group.

Among patients who had combined pancreatectomy, the majority received distal pancreatectomy (DP) (n = 24, 60%), followed by pancreaticoduodenectomy (PD) (n = 8, 20%), and partial pancreatectomy (PP) (n = 8, 20%). Compared to PP group, severe morbidity in the PD group was significantly higher (p = 0.024), while there was no difference between DP and PP groups (p = 0.468) (Table 4).

Table 2. Postoperative complications

Cases (n)	64 (100%)
Overall morbidity	34 (53.1)
Severe morbidity (Clavien- Dindo III–IV or POPF Grade B and C*)	14 (21.9)
Postoperative Pancreatic Fistula	12 (18.8)
Anastomotic leakage	4 (6.3)
Intraabdominal deep abscess	4 (6.3)
Postoperative Hemorrhage Grade C	2 (3.1)
Acute renal failure	1 (1.6)
Reoperation	2 (3.1)
Postoperative death (day 90)	0

3.3. DFS and OS

The estimated OS and RFS at 5 years were 90.0% and 86.6%, respectively. Eight patients experienced tumor recurrence. Univariate analysis showed that tumor size, mitotic rate and postoperative imatinib therapy was associated with tumor recurrence. However, only high mitotic rate was proved to be independent risk factor by Multivariate analysis (Table 5).

4. Discussion

Locally advanced GISTs represent a clinical challenge, and the prognosis of unresectable cases was extremely poor. In our study cohort, 64 patients underwent MVR for locally advanced GISTs. The 5-year OS and DFS were 90% and 86.6%, which confirmed that MVR could do benefit to selected patients.

In this series, the common indications for MVR include downsizing failure, emergent operations and judgment difficulty. Firstly, some locally advanced GISTs cannot be downsized successfully by neoadjuvant imatinib. The reported response rate of SD/PD cases ranged from 18.6-83% in different studies (*3-5*). For patients of downsizing failure, surgical complexity has not decreased, and MVR is unavoidable. Secondly, GISTs may present with acute abdomen, obstruction, perforation or rupture and peritonitis. In the event of such an emergency, MVR may be forced. According to a

Table 4. Analysis of different type of pancreatectomy for severe morbidity

Items	Severe morbidity	Non-severe morbidity	P-value
No. of patients	13	27	
Partial pancreatectomy	1	7	-
Distal pancreatectomy	6	18	0.468
Pancreaticoduodenectomy	6	2	0.024

Table 3. Univariate and multivariate analysis of risk factors for overall and severe morbidity

Items	Overall Morbidity group	Non-morbidity group	Univariate analyses P-value	Multivariate analyses P-value	Severe morbidity group	Non-severe morbidity group	Univariate analyses P-value	Multivariate analyses P-value
No. of patients	34	30			14	50		
Age (years)	57.7	57.3	0.933	-	56.7	57.7	0.811	-
Sex (male)	12 (35.2%)	18 (60.0%)	0.143	-	6 (42.9%)	24 (48.0%)	0.529	-
Preoperative Imatinib	10 (29.4%)	16 (53.3 %)	0.003	0.048	7 (50%)	19 (38.0%)	0.347	-
Tumor site			0.316	-			0.546	-
Stomach	16 (47.1%)	16 (53.3%)			6 (42.9 %)	26 (52.0%)		
Small intestine	18 (52.9%)	14 (46.7 %)			8 (57.1%)	24 (48.0%)		
Mean tumor size (cm)	9.9	12.5	0.008	0.065	8.6	11.8	0.054	-
Operative factors								
Resected organ ≥ 3	6 (17.6%)	10 (33.3%)	0.285	-	4 (28.6%)	12 (24.0%)	0.727	-
+Pancreatectomy	30 (88.2%)	10 (33.3%)	0.247	-	13 (92.9%)	27 (54.0%)	0.025	0.003
+splenectomy	16 (47.1%)	12 (40.0%)	0.950	-	6 (42.9%)	22 (44%)	0.939	
+colectomy	16 (47.1%)	12 (40.0%)	0.617	-	11 (78.6%)	17 (34.0%)	0.048	0.016
Operation time (min)	350	296	0.381	-	403	302	0.001	0.014
Blood loss (mL)	819	467	0.976	-	1000	557	0.045	0.272

Table 5. Univariate and multivariate analysis of RFS

Items	Non-recurrence group	Recurrence group	Univariate analyses *P*-value	Multivariate analyses *P*-value
No. of patients	56	8		
Age (yrs)	56.8	63.0	0.180	-
Sex (male)	29 (51.2%)	1 (12.5%)	0.067	0.082
Preoperative Imatinib	22 (39.3%)	4 (50%)	0.850	
Emergency	4 (7.1%)	2 (25%)	0.130	0.099
Tumor site			1.000	-
Stomach	28 (50%)	4 (50%)		
Small bowel	28 (50%)	4 (50%)		
Tumor size (cm)			0.026	0.418
< 15	48 (85.7%)	4 (50%)		
≥ 15	8 (14.3%)	4 (50%)		
Mitotic rate per 50 HPF			0.006	0.044
> 5	12 (21.4%)	6 (75%)		
≤ 5	44 (78.6%)	2 (25%)		
Microscopic organ involvement	18 (32.1%)	2 (25%)	0.685	
Postoperative Imatinib	40 (71.4%)	2 (25%)	0.020	0.206
Overall morbidity	31 (55.4%)	3 (37.5%)	0.351	-
Severe morbidity	11 (19.6%)	3 (37.5%)	0.264	-
Operative factors				
Resected organ ≥ 3	14 (25%)	2 (25%)	1.000	-
Operation time (min)	325	326.5	0.966	-
Blood loss (mL)	663	450	0.405	-

report by Magdy, among 92 GISTs-related emergencies, 2 patients required MVR (*9*). Finally, in some cases, although downsized successfully, the tumor is still close to neighboring organs. It is difficult to make a sound judgment whether the tumor is adherence or infiltration of the surrounding organs. To ensure complete resection and avoid iatrogenic tumor rupture, en bloc resection of adjacent organs is still required (*10*). Other less common causes of MVR in this study include being misdiagnosed as primary retroperitoneal sarcoma, intolerance to imatinib and wide-type GISTs. In addition, microscopic contiguous organ involvement could be observed in more than 30% cases, proving that MVR is sometimes necessary to achieve complete resection.

Established prognostic factors for GISTs are tumor site, tumor size, mitotic count and tumor rupture (*11-13*). However, on multivariate analysis of this study, only high mitotic count was associated with recurrence. More tumors originated in the duodenum and the larger tumor volumes was observed in this series, which might be one of the reasons for the discrepancy. DeMatteo and colleagues proved that size > 10 cm was independently prognostic factors of RFS for GISTs (*13*). However, most tumors in our study were larger than 10cm. therefore, the analysis value we chose was 15 cm. On univariate analysis, larger tumor size was associated with tumor recurrence, but not proved by multivariate analysis.

Tumor rupture was considered to be associated with a substantially higher risk of tumor recurrence. Patients with intraoperative rupture of GIST into the peritoneal cavity had a risk of recurrence (*14*). In the present study, there was no tumor rupture occurred and the 5-year RFS in patients who underwent MVR for locally advanced GISTs was excellent, which might be due to the aggressiveness of MVR. Firstly, we do not attempt to separate the tumor from the surrounding involvement organs in order to avoid exposing the tumor and make a resection similar to "compartment resection". Secondly, an "anterior approach" was routinely used to avoid compression and rotate the tumor. Undoubtedly, such an "no-touch" surgical technique could minimize the risk of iatrogenic tumor rupture.

In this study, MVR was proved to be a more complicated surgical procedure The median number of resected contiguous organ for each patient was 2, and half of the tumors originated in the duodenum and the mean tumor size was 11.1 cm, leading a result in much higher proportion of combined pancreatectomy. The morbidity of pancreatectomy remains high even in high-volume centers. In a report from the Transatlantic RPS Working Group, the overall morbidity was 64% for patients with soft tissue sarcoma who underwent surgery requiring pancreas resection (*15*). Therefore, the overall morbidity in this cohort was higher than reports in the literature (*16-18*). The benefits of MVR must be balanced against the risks associated with the operation.

Fortunately, preoperative imatinib could significantly reduce the overall morbidity. Most GISTs are fragile and hypervascular, leading the high risk of bleeding and tumor rupture. Imatinib can reduce the blood supply and make the tumor robust, which may facilitate surgical procedure and reduce postoperative complications (*17*). In a retrospective study of 25 advanced GISTs patients who underwent surgery after preoperative imatinib therapy, no postoperative complications appeared (*18*). In a prospective phase II study, designed to evaluate safety and efficacy of neoadjuvant imatinib for patients with advanced primary and metastatic/recurrent operable

GISTs, the complications of surgery were also minimal (*4*). Based on these results, preoperative imatinib therapy should be recommended whenever possible.

Our data showed that pancreatectomy was associated with significant severe morbidity of MVR. Twelve (18.8%) patients had a clinically relevant (grade B or C) POPF, which is slightly higher than data of ISGPF (*19*). It might be related to normal pancreatic duct, soft pancreas tissue and imatinib associated edema for GISTs. Two patients had a postoperative hemorrhage (grade C, 3.1%) which was comparable to the results in the literature (*20*) and both of them had undergone a combined PD. Compared to partial pancreatectomy, PD was more complicated and required more operation time, which was another independent risk factor for severe morbidity after MVR in this study. Therefore, in our center PD should be thoroughly discussed and the patient should be fully informed about the risks before surgery.

Furthermore, nearly 40% of patients had combined colectomies in the cohort. Addition of colectomy to pancreatectomy could aggravate the severity of pancreatic fistula. Swchartz (*21*) reported that the 90-day morbidity and mortality rate in patients of simultaneous pancreatectomy with colectomy were 61% and 14% respectively, which was much higher than pancreatectomy alone (42% and 3%, $P < 0.01$). To mitigate mortality risk, a diverting loop ileostomy was selectively done for patients of MVR requiring combined colectomy. By reducing the enteral stream across the anastomosis, the morbidity associated with a colonic leak could potentially be avoided. Although the patients had to undergo stomal closure three months later, no fistula-related perioperative deaths occurred in this series.

In conclusion, compared to systemic therapy alone, the outcome of locally advanced GISTs after MVR was more favorable. Despite the high overall morbidity, the postoperative severe morbidity and mortality of MVR were acceptable. Preoperative imatinib therapy should be recommended whenever possible. Combined pancreatectomy and colectomy are associated with significant postoperative severe morbidities. PD should be thoroughly discussed and be subject to MDT approach before surgery.

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