Brief Report

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Organ-preserving surgery for locally advanced duodenal gastrointestinal stromal tumor after neoadjuvant treatment

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Summary **This report aims to investigate the feasibility and outcomes of neoadjuvant imatinib mesylate (IM) administration followed by organ-preserving surgery (OPS) for patients with locally advanced duodenal gastrointestinal stromal tumor (GIST). Between 2012 and 2015, 10 consecutive patients with locally advanced duodenal GISTs were treated in Peking University Cancer Hospital. Multidisciplinary assessment was implemented, and pancreaticoduodenectomy (PD) was initially indicated as the most probable surgical procedure for all 10 patients. To attempt to create opportunities of less-invasive OPS for patients, neoadjuvant IM was administered followed by radical resection. All data were prospectively collected, and the short- and long-term outcomes of the treatment strategy were analyzed. The median treatment duration of neoadjuvant IM administration was 5 mo (range 2-18 mo). Significant tumor shrinkage (from 9.2 to 5.9 cm on average) was observed in all patients, and partial response was achieved in eight patients (80.0%) according to the Response Evaluation Criteria in Solid Tumors 1.1. No tumor perforation occurred, and nine patients (90.0%) underwent successful OPS with four different operation types. Postoperative morbidity rate of OPS was 55.6% (5/9), and no mortality occurred. After a median follow-up of 36 mo, one patient developed multiple distant metastases, but no local recurrence was observed. For long-term follow-up, patients who underwent OPS did not show any degradation in quality of life, whereas the patient who underwent PD suffered weight loss of ~10 kg. In conclusion, in patients with locally advanced duodenal GISTs, neoadjuvant IM administration followed by OPS is a feasible treatment strategy which leads to favorable short- and long-term outcomes.**

Keywords: Organ-preserving surgery, duodenal gastrointestinal stromal tumor, imatinib mesylate, pancreaticoduodenectomy, neoadjuvant therapy

1. Introduction

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor arising in the gastrointestinal tract. GISTs occur most frequently in the stomach (50-60%), followed by the small intestine (~30%) (*1*). Duodenal GISTs are relatively uncommon and comprise ~5% of all GISTs, but represent ~20% of primary small intestine cases (*2*).

More than 80% of GISTs harbor *c-KIT* or platelet-derived growth factor receptor *(PDGFR)A* gene mutations (*3,4*). Imatinib mesylate (IM), an inhibitor of *c-KIT* and *PDGFRA*, can effectively reduce tumor size and improve prognosis (*5*). However, IM treatment cannot completely replace surgery, and complete surgical resection with clear margins remains the only curative approach for resectable GISTs.

Pancreaticoduodenectomy (PD) is the standard surgical procedure for malignant tumors in the periampullary area. Despite advances in surgical

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techniques and perioperative management, the rates of postoperative complications (30-50%) and mortality (1-7.8%) for PD remain high (*6*). For these reasons, and because of its significant effect on long-term quality of life, less invasive organ-preserving surgery (OPS) might be more beneficial for patients with low-grade malignancies such as duodenal GISTs. GISTs frequently show expansive growth with a clear border, and they rarely exhibit lymph node metastasis, for which complete excision with negative margins is indicated; therefore, extensive resection is usually not required.

However, for advanced duodenal GISTs that exhibit large tumor size, the separation of the pancreas and the major papilla from the tumor is complicated. These features hamper OPS, and PD remains the most common procedure in patients with locally advanced duodenal GISTs. The treatment strategy of neoadjuvant IM followed by OPS was designed specifically for these patients. It is expected that IM-induced tumor shrinkage to produce clearer borders would facilitate the successful application of OPS in patients who were initially indicated for PD.

The objective of the present study was to evaluate the feasibility and short- and long-term outcomes of this treatment strategy in patients with locally advanced duodenal GISTs.

2. Materials and Methods

2.1. *Study population*

We reviewed the prospectively collected data of 10 consecutive patients with locally advanced duodenal GISTs who were treated with preoperative IM followed by radical resection from August 2012 to September 2015 at the Department of Hepato-Pancreato-Biliary Surgery, Peking University Cancer Hospital & Institute, Beijing, China. All patients were definitively diagnosed with GIST by preoperative endoscopic or abdominal ultrasound-guided fine needle aspiration. The incidence of mutations (*c-KIT* 9, 11, 13 and 17, and *PDGFRA* 12 and 18) was evaluated by sequencing of polymerase chain reaction products, as described previously (*7*).

Data concerning clinical information, surgical procedures, pathological findings, complications after surgery, and long-term outcomes were extracted from patient records. Written informed consent, as required by the Institutional Review Board of Peking University Cancer Hospital & Institute, was obtained from all patients.

2.2. *Preoperative treatment*

Following a discussion among the surgeons, oncologists, radiologists and pathologists, all cases were classified as advanced stage and PD was initially indicated as the most probable surgical procedure for all 10 patients. After careful multidisciplinary assessment, IM (400 mg/d) was administered preoperatively in all patients to reduce tumor burden. Thereafter, tumor response was evaluated every 2 mo according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (*8*), and surgical resection was performed when tumor shrinkage reached a plateau.

2.3. *Surgical procedures*

After exploratory laparotomy and confirming the possibility of R0 resection, the right part of the gastrocolic ligament was divided and the Kocher procedure was performed to expose the second portion of the duodenum and the pancreatic head. When necessary, the Cattell-Braasch maneuver was performed to expose the third portion of the duodenum.

The position of the major papilla and its relationship to the tumor were subsequently determined by careful palpation and insertion of a tube in the cystic duct after cholecystectomy. If tumor invasion of the major papilla was observed, PD was performed. However, if conservation of the major papilla was possible, one of the four OPS procedures was performed (Figure 1). The decision for resection type was made at the discretion of the operating surgeon. Type 1, for tumors located at the second portion, the area of the duodenal wall containing the base of the tumor was completely resected and primary closure was performed. Type 2, for tumors located at the medial wall of the second portion, when separation of the pancreas from the tumor was complicated. *En-bloc* radical resection including partial duodenal wall and partial pancreatic parenchyma resection were performed, and to avoid intractable postoperative pancreatic fistula formation, as well as for primary closure of the duodenal wall, side-to-side anastomosis of the pancreatic wound surface with the jejunum was performed by running suturing via Roux-en-Y reconstruction. Type 3, for large tumors located at the third portion, segmental resection of the third and fourth portions, and end-to-end anastomosis between the residual duodenum and the proximal jejunum were performed. Type 4, for large tumors located at the border of the second and third portions that invaded the head of the pancreas, when the Wirsung duct had to be transected but the major papilla and intrapancreatic common bile duct could be preserved, *en-bloc* radical resection, including the third and fourth portions, and partial pancreatic parenchyma resection were performed. The pancreatic wound surface was anastomosed to the jejunum by a Wirsung duct-to-mucosa anastomosis, and the duodenojejunal end-to-side anastomosis in the same jejunal loop was also performed.

Systematic nodal dissection around the pancreatic head was not performed routinely. All procedures were performed by the same senior hepato-pancreato-biliary surgeon (CY Hao). The resected specimens

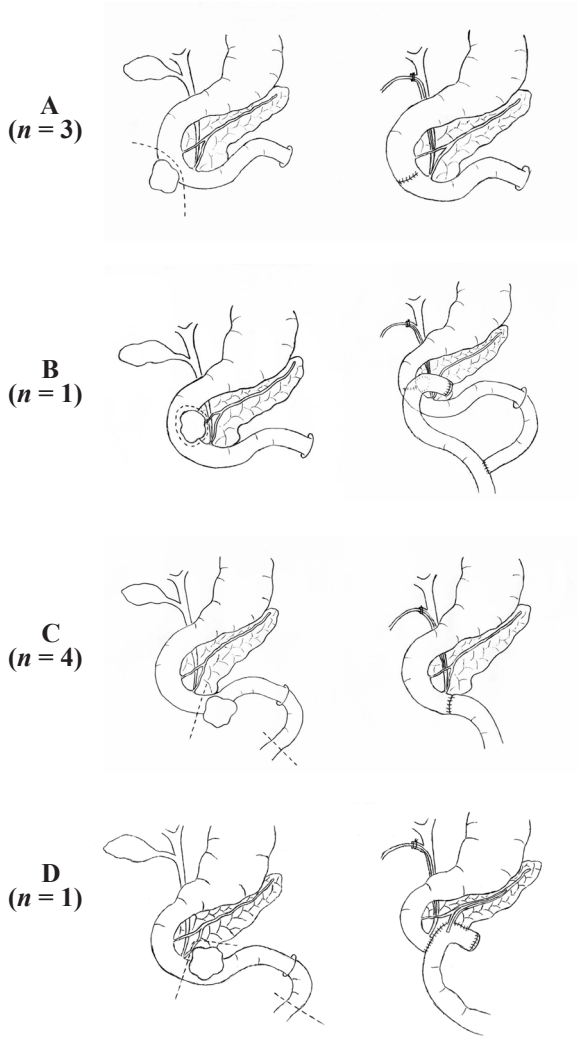

Figure 1. The four OPS procedures. (A) Type 1: for tumors located at the second portion, the area of the duodenal wall containing the base of the tumor was completely resected (left), and primary closure was performed (right). **(B)** Type 2: for tumors located at the medial wall of the second portion, *en-bloc* radical resection including partial duodenal wall and partial pancreatic parenchyma resection were performed (left). Primary closure of the duodenal wall and side-to-side anastomosis of the pancreatic wound surface with the jejunum was performed by runningsuturing *via* Roux-en-Y reconstruction (right). **(C)** Type 3: for large tumors located at the third portion, segmental resection of the third and fourth portions (left), and end-to-end anastomosis between the residual duodenum and proximal jejunum was performed (right). **(D)** Type 4: for large tumors located at the border of the second and third portions that invaded the head of the pancreas, when the Wirsung duct had to be transected but major papilla and intrapancreatic common bile duct could be preserved, *en-bloc* radical resection, including the third and fourth portions, and partial pancreatic parenchyma resection were performed (left). The pancreatic wound surface was anastomosed to the jejunum by a Wirsung duct-to-mucosa anastomosis, and the duodenojejunal end-to-side anastomosis in the same jejunal loop was also performed (right).

were examined pathologically. Risk stratification was determined according to the revised National Institutes of Health (NIH) classification (*9*).

2.4. *Postoperative complications and follow-up*

Complications were recorded and classified according to the criteria proposed by Clavien *et al* (*10*); grade ≥ 2 complications were recorded. Postoperative pancreatic fistula (POPF) was defined according to the International Study Group on Pancreatic Fistula recommendations (*11*); grade ≥ B POPF was recorded. Delayed gastric emptying (DGE) was defined as prolonged aspiration of 500 mL/d from the nasogastric tube for ≥ 10 postoperative days, the need for reinsertion of a nasogastric tube, or the failure to maintain oral intake by postoperative day 14 (*12*).

Postoperative adjuvant therapy with IM at 400 mg/d was administered in all cases. Systemic follow-up included postoperative abdominal ultrasound or computed tomography scanning at 3-mo intervals. Long-term quality of life data regarding general health, weight loss, gastrointestinal symptoms, and dietary restrictions were obtained.

3. Results and Discussion

Ten patients with locally advanced duodenal GISTs (6 men and 4 women; median age, 50 years; range, 43-65 years) were enrolled in the analysis. Tumors were diagnosed based on chief complaints (Table 1). The primary tumor was located at the second portion of the duodenum in five cases, at the third portion in three cases, and at the border of the second and third portions in two cases. The most common c-KIT mutation was the exon 11 deletion mutation (8/10 patients), whereas two patients harbored the exon 9 duplication (Table 1).

Preoperative IM was administered in all 10 patients for 2-18 mo (median, 5 mo). Significant tumor shrinkage was observed in all patients, with a maximum mean diameter decrease from 9.2 cm (range, 4.7-16.0 cm) to 5.9 cm (range, 3.0-12.8 cm) (Table 1, Figure 2). No tumor perforation occurred. According to RECIST 1.1 criteria, eight cases (80.0%) achieved a partial response (PR), and two cases had stable disease (SD) with < 30% tumor shrinkage. Surgical resection was performed at a mean of 22 d (range, 14-36 d) after IM discontinuation.

Nine patients (90.0%) underwent successful OPS (Table 2). In one patient, PD was performed because the major papilla was invaded by the tumor, which failed to be separated. R0 resection was achieved in all cases. For OPS, the median estimated blood loss was 450 mL (range, 100-800 mL), and the median operating time was 385 min (range, 273-540 min). None of the patients received intraoperative blood transfusion. For the patient undergoing PD, the blood loss was 400 mL, and operating time was 380 min. Overall, 4 units of red blood cells were transfused because of preoperative anemia.

The mean maximal tumor diameter of all surgical specimens was 6.8 cm (range, 3.5-14.0 cm). The mitotic counts and Ki67 proliferation indices of all specimens are shown in Table 2. All 10 cases were classified as high-risk at the time of surgical resection. Surgical

Table 1. Clinicopathological characteristics and preoperative treatment of patients with advanced duodenal GIST

No.	Sex/age (yr)	Chief complaint	Gene mutation	Tumor size (cm) pre-/post-IM	IM treatment duration (mo)	Response (RECIST 1.1)	Revised NIH classification
1	F/44	Abdominal pain	Exon 11 Del 569-576	13.5/7	18	PR	High
2	M/50	Asymptomatic	Exon 11 Del 559-574	4.7/3	4	PR	High
3	M/43	Black stool	Exon 11 Del 553-574	6.7/4.6	4	PR	High
4	F/50	Abdominal pain	Exon 11 Del 557-571	5.0/3.5	2	PR	High
5	M/60	Abdominal discomfort	Exon 11 Del 563-571	6.5/4.1	6	PR	High
6	M/44	Abdominal discomfort	Exon 11 PM V559D	16/12.7	6	SD	High
7	F/50	Black stool	Exon 9 Dup 502-503	8/4.7	8	PR	High
8	M/44	Black stool	Exon 11 Del 566-575	11/6.5	4	PR	High
9	M/65	Black stool	Exon 11 Del 557-571	8/3.7	17	PR	High
10	F/64	Abdominal pain	Exon 9 Dup 502-503	12/9	4	SD	High

F, female; M, male; Del, deletion; PM, point mutation; Dup, duplication.

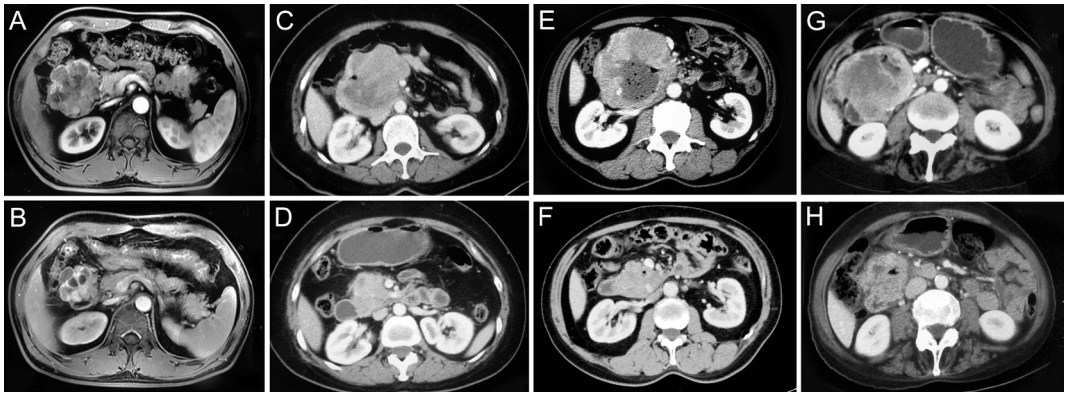

Figure 2. Comparison of radiological appearance before and after preoperative IM treatment for advanced duodenal GIST. (A, B): A 6.7-cm lesion at the second portion **(A)** reduced to 4.6 cm after 4 mo preoperative treatment **(B)**. A type 2 surgical procedure was performed. **(C,D)**: An 8.0-cm lesion at the third portion **(C)** reduced to 4.7 cm after 8 mo preoperative treatment **(D)**. A type 3 surgical procedure was performed. **(E,F)**: An 11.0-cm lesion at the border of the second and third portions **(E)** reduced to 6.5 cm after 4 mo preoperative treatment **(F)**. A type 4 surgical procedure was performed. **(G,H)**: A 12.0-cm lesion at the third portion **(G)** reduced to 9.0 cm after 4 mo preoperative treatment **(H)**. Because the major papilla was invaded by the tumor, PD was performed.

Table 2. Surgical characteristics, pathological findings, and short and long-term outcomes of patients with advanced duodenal GISTs

No.	Location	Surgical procedure	OT (min)	EBL (mL)	Mitotic counts (/50 HPF)	Ki67 (%)	POPF/GI leakage/DGE	Recurrence or metastasis	Status/follow-up (mo)
1	D3	Type 3	390	500	5-10	5	N/N/Y	None	Alive/36
2	D2	Type 1	274	200	> 10	10	N/N/N	None	Alive/50
3	D2	Type 2	356	700	< 5	5	N/N/N	None	Alive/44
4	D2/3	Type 3	273	100	5-10	5	N/N/N	None	Alive/47
5	D2	Type 1	353	800	> 10	60	N/Y/N	Liver (6 mo)	Dead/17
6	D2	Type 1	405	600	> 10	10	Y/N/N	None	Alive/36
7	D3	Type 3	420	300	> 10	10	Y/N/Y	None	Alive/17
8	D2/3	Type 4	540	200	< 5	3	Y/Y/N	None	Alive/16
9	D2	Type 3	458	550	5-10	10	N/N/N	None	Alive/16
10	D3	PD	380	400	< 5	15	Y/N/N	None	Alive/41

D2, second portion of the duodenum; D3, third portion of the duodenum; OT, operating time; EBL, estimated blood loss; HPF, high-power field; GI, gastrointestinal; N, no; Y, yes.

margins were negative in all patients.

Postoperative morbidity rate of OPS was 55.6% (5/9). POPF, gastrointestinal leakage, and DGE were the most common complications (Table 2). Two patients were successfully treated with ultrasound-guided percutaneous drainage, and others were resolved after conservative therapy consisting of complete drainage and antibiotic therapy. In the patient who underwent PD, POPF was observed and was successfully treated with ultrasound-guided percutaneous drainage. Subsequent surgery was not required in any patient, and there was no perioperative mortality. The median duration of hospital stay was 19 d (range, 13-36 d).

The median follow-up duration was 36 mo (range, 16-50 mo). At 6 postoperative months, multiple liver and peritoneal metastases were detected in one patient who underwent OPS, and second-line treatment with sunitinib was administered. The patient was dead at 17 postoperative months. The remaining nine patients were alive with no evidence of local recurrence or metastasis at the end of the follow-up period (Table 2).

OPS was not associated with late comorbidity such as reflux cholangitis, pancreatitis, weight loss, or diarrhea. In addition, none of the patients who underwent OPS reported any degradation in quality of life. The patient who underwent PD reported a weight loss of ~10 kg. There were no IM-related grade 3 or 4 adverse events.

The outcomes of limited resection or pancreas-sparing duodenectomy of duodenal GISTs (*13,14*), and the results of neoadjuvant IM therapy in advanced GISTs (*15,16*) have been reported. However, to the best of our knowledge, the present study is the first to describe preoperative IM as neoadjuvant therapy followed by OPS for patients with locally advanced duodenal GISTs who would otherwise require PD.

Duodenal GISTs frequently involve the second portion of the duodenum and less often the third, fourth, and first portions (*17*). With less invasiveness and a low incidence of nodal metastasis (*18*), the goal of surgery for GISTs is complete tumor resection with negative surgical margins. Therefore, extensive resection including nodal dissection is usually not required, and OPS presents an attractive alternative to PD for duodenal GISTs.

IM is the first globally approved effective nonsurgical treatment for inoperable or metastatic GIST with a response rate of > 80% (*5,19*). IM has been approved for adjuvant therapy in patients with GIST who have a high risk of postoperative recurrence (*20,21*). Subsequently, the development of an IM-based neoadjuvant treatment strategy has been proposed (*22*). In selected cases of locally advanced GIST, IM facilitates resection and decreases surgical morbidity by reducing the need for extensive resection and the perioperative risk of tumor rupture (*15,23*).

Candidates for preoperative IM include patients who may benefit from preoperative tumor downstaging, and such selection processes require careful multidisciplinary assessment. This strategy is especially attractive in difficult anatomical locations (duodenum, distal rectum, or gastroesophageal junction) where resection of the primary tumor may cause significant morbidity or functional deficits. Therefore, patients with locally advanced duodenal GISTs, in which PD is considered as the standard surgical approach, represent ideal candidates for preoperative IM therapy. Tumor shrinkage facilitates visualization of the relationship of the tumor with the major papilla and pancreatic parenchyma, thereby enhancing the likelihood of successful OPS. In the present study, preoperative IM induced tumor shrinkage in all cases, with most patients demonstrating a PR and undergoing successful OPS. Although, previous studies have shown that 3-5% of patients with advanced GISTs who were treated with IM had gastrointestinal and tumor hemorrhage that required earlier surgical intervention (*5*), in the present study IM was well tolerated with no cases of tumor perforation, hemorrhage, or grade 3/4 adverse events.

Because of the acquisition of additional activating *c-KIT* or *PDGFRA* mutations in tumor clones, which usually accounts for secondary resistance, a refractory response to IM occurs at a median of 2 years after treatment initiation (*24*). Therefore, surgery cannot be completely replaced, and surgical intervention is required for resectable cases following tumor shrinkage. The optimal duration for preoperative IM therapy is usually 4-12 mo (*15*). At this time, a plateau in tumor shrinkage is usually seen and the risk of developing secondary resistance to IM is still low. In our series, the mean duration of IM was within these suggested boundaries.

Johnston *et al* (*25*) supposed that recurrence of duodenal GISTs was mostly dependent on the tumor biology rather than the surgical approach. A retrospective review of 114 patients from the French Sarcoma Group (*26*) revealed that limited resection results in similar survival and lower morbidity rates compared with PD. In the present study, local recurrence was not observed in the median 36-mo follow-up. At 6 postoperative months, patient 5 developed liver and peritoneal multiple metastases. It is worth noting that the Ki67 index reached up to 60%. This might explain the poor prognosis and confirm that the recurrence in that case was dependent on tumor biology rather than surgical approach. POPF, gastrointestinal leakage and DGE occurred in three, two and two cases respectively, but all cases were successfully treated with ultrasound-guided percutaneous drainage or conservative therapy, indicating the acceptable safety of OPS. Furthermore, the patients who underwent OPS have demonstrated good quality of life thus far, while the patient who underwent PD suffered obvious weight loss, suggesting that OPS might be more advantageous than PD in terms of long-term quality of life.

Indications for OPS depend not only on tumor size, but also on tumor location and proximity to nearby structures (pancreatic duct, distal common bile duct, and major papilla). Because of proximity to these structures, OPS is a technically demanding procedure. In the present study, the major indication for OPS was successful preservation of the major papilla and intrapancreatic common bile duct. Some studies (*13*) have suggested that, to achieve adequate tumor clearance, conventional PD should be performed in cases of partial pancreatic parenchyma invasion. However, in our experience, this may not be a contraindication to OPS. Resection of adequate partial pancreas parenchyma followed by anastomosis of the pancreatic wound surface to the jejunum (type 2 procedure), and even transection of the Wirsung duct and duct-to-mucosa anastomosis (type 4 procedure) resulted in favorable progression-free survival. It is worth noting that in patient 10, although obvious tumor shrinkage was seen, OPS was not performed because of tumor invasion to the major papilla.

Various OPS techniques for duodenal GISTs have been described (*13,14,27,28*), however, to the best of our knowledge, the type 4 procedure is a creative surgical procedure that has not been reported before. Besides the four techniques described in the present study, for large tumors involving the second portion of the duodenum, where the resulting defect is too large to close, both proximal segmental duodenectomy and Roux-en-Y anastomosis of the duodenal defect with the jejunum have been proposed. Pancreatic head resection with segmental duodenectomy has been reported as OPS for benign or low-grade malignant tumors of the pancreatic head (*29*). However, OPS with reimplantation of the major papilla is technically demanding, and carries a higher morbidity risk. Therefore, in our institution, we perform PD when tumor invasion prevents major papilla preservation.

The study had some limitations such as small sample size and short follow-up period. However, our results indicate that preoperative IM effectively downsizes the tumor in patients with locally advanced duodenal GISTs, facilitating complete tumor resection via less invasive OPS.

In conclusion, in patients with locally advanced duodenal GISTs, neoadjuvant IM administration followed by OPS is a feasible treatment strategy that provides favorable short- and long-term outcomes.

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