

Duodenal Gastrointestinal Stromal Tumors (GISTs): Arguments for Conservative Surgery

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Received: 9 August 2012 / Accepted: 29 October 2012 / Published online: 15 November 2012
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Abstract

Introduction Gastrointestinal stromal tumors (GISTs) of the duodenum are rare. We sought to evaluate the postoperative courses and long-term outcomes of conservative surgery (CS) versus pancreaticoduodenectomy (PD) for patients with non-metastatic duodenal GISTs.

Methods Seventeen patients underwent surgery for duodenal GISTs between January 2000 and January 2012; 11 patients underwent CS (CS group), and six patients underwent a PD (PD group).

Results Mortality was similar between the two groups. Patients in the PD group had longer operative times, more tumors located on the pancreatic side of the duodenum, higher rates of post-operative complications including postoperative pancreatic fistulas, and a longer hospital stay, when compared with patients of CS group. All tumors were resected with clear surgical margins (R0 resection). The median disease-free survival times were not different.

Conclusion CS was safe and provided similar oncologic outcomes as PD. CS should be the procedure of choice in patients with GIST that does not involve the pancreatic side of the duodenum.

Keywords Gastrointestinal stromal tumors · Duodenal neoplasm · Segmental duodenectomy · Pancreaticoduodenectomy · Imatinib mesylate

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Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors that arise in the gastrointestinal tract^{1,2} and were first described by Mazur and Clark in 1983.³ In the 1990s, expression of the c-kit proto-oncogene (CD 117) by immunohistochemistry helped clinicians to distinguish GISTs from other soft tissue tumors, such as leiomyomas and myoblastomas.⁴ GISTs can develop all along the digestive tract and are found most frequently in patients aged 40 years and over, with a worldwide incidence of approximately 15 per one million persons.^{1,2,4} Duodenal GISTs constitute 5 % of all GISTs and represent 10 % to 30 % of all malignant duodenal tumors. Because GISTs rarely metastasize to lymph nodes,¹ resection without extended lymphadenectomy remains the gold standard. However, the treatment of duodenal GISTs is challenging due to important neighboring anatomical structures (pancreatic head, ampulla of Vater, common bile duct, etc.). The surgical management is therefore a balance between pancreaticoduodenectomy (PD) and conservative surgery (CS).⁵

This retrospective analysis was designed to evaluate the postoperative courses and the long-term outcomes of CS versus PD for patients with non-metastatic duodenal GISTs.

Materials and Methods

Patient Selection

Using an anatomopathological multicenter database, the medical records of patients who underwent surgery for a duodenal GIST from January 2000 to January 2012 were reviewed. Only patients with immunohistologically proven duodenal GIST (i.e., expression of the CD117 c-kit receptor) were included in the study. To study a homogeneous population, none of the studied patients received targeted neo-adjuvant therapy before surgery. Thus, 17 patients were included in the study. Staging of the disease and precise location of the tumor were assessed using clinical examination, thoraco-abdominal computed tomography, endo-ultrasonography, and eventually, pancreatic magnetic resonance imaging (MRI). The patients were divided in two groups according to surgical procedure (PD or CS): PD group ($n=6$) and CS group ($n=11$).

Surgery

Operations were performed via a subcostal or midline incision. The first stage of the surgery was an extended Kocher maneuver for tumors lying in the second or third portion of the duodenum. According to preoperative imaging and the intra-operative location of the tumor (i.e., distance from the ampulla of Vater assessed by intraoperative ultrasonography and eventually opening of the second portion of the duodenum), a CS or a PD was performed.

Reconstruction during PD was achieved using a pancreaticojejunostomy or a pancreaticogastrostomy according to surgeon and center preferences. Drainage was achieved using Penrose or closed-suction drains.

CS included wedge or segmental resections of the duodenum. When a wedge resection was performed, the duodenal defect was closed primarily. If direct suture of the duodenum was not possible, a Roux-en-Y duodenojejunostomy was performed.

After segmental resection of the duodenum, digestive continuity was achieved by an end-to-end duodenojejunostomy. One patient had re-implantation of the papilla in a jejunal patch during segmental resection of the second portion of the duodenum.

Prophylactic octreotide was not routinely used in either the PD or CS group.

Data Collection

The following data were retrieved to evaluate the postoperative outcomes and long-term oncologic results of each procedure: sex, age, American Society of Anesthesiologists (ASA) score,⁶ circumstances of diagnosis (presence or absence of symptoms), location of the tumor (first (D1), second (D2), third (D3), or fourth (D4) portion of the duodenum), surgical procedure (PD or CS), operative time (minutes), perioperative transfusion (number of patients requiring red blood cell transfusions within 30 days after surgery), morbidity according to the Clavien–Dindo classification,⁷ post-operative pancreatic fistula (POPF) according to the International Study Group on Pancreatic Fistula classification,⁸ mortality (within 30 days after surgery or before hospital discharge), duration of hospital stay (days), tumor size (the largest diameter of the tumor; centimeters), mitotic count (50 high-power fields (HPFs) on a microscope with wide-field oculars), and margin resection (R0 or R1/R2 resection). Size and mitotic count were used to determine the prognosis of the GISTs according to the Miettinen classification:⁹ very low, low, intermediate, or high risk of recurrence.

Follow-up data included the date of the most recent follow-up or at 01 June 2012, the censor date. The status of the patient (alive without disease, alive with disease, dead with disease, or dead without disease) and cause of death (disease recurrence or other cause) were noted. Categorical variables are described in terms of frequency and percentages. The distributions of continuous variables are described as the median (range). Disease-free survival was analyzed using the Kaplan–Meier method.

Results

Patient Characteristics

Patient characteristics are listed in Table 1. The median age was 56 years (range, 38–75 years). The PD group had a greater proportion of males than the CS group. One GIST (5 %) was located in D1, ten (59 %) in D2, three (18 %) in D3, and three (18 %) in D4.

Surgery and Postoperative Outcome

Surgical data are summarized in Table 2. The median operating time was longer in the PD group (405 versus 90 min, respectively). No difference was noted in perioperative transfusions. Post-operative outcomes are summarized in Table 2. Complications occurred in ten patients (59 %). The overall morbidity rate was higher in the PD group than in the CS group (100 % versus 36 %). Clavien–Dindo grade

Table 1 Comparison of demographic data between patients treated by PD or CS

Characteristics	All patients		PD group		CS group	
Patients	17		6	35 %	11	65 %
Median age (range)	56	(38–75)	62	(39–73)	54	(38–75)
Sex						
Men (%)	8	(47)	5	(83)	3	(27)
Women (%)	9	(53)	1	(17)	8	(73)
ASA classification						
1–2 (%)	12	(71)	3	(50)	9	(82)
3 (%)	5	(29)	3	(50)	2	(18)
Symptoms (%)	10	(59)	3	(50)	7	(64)
Anemia (%)	6	(35)	2	(33)	4	(36)
Pain (%)	2	(12)	0		2	(18)
Mass (%)	2	(12)	1	(17)	1	(9)

I/II and grade III/IV complications were similar between the two groups. Mortality rates were not significantly different between the PD group and CS group (17 % versus 0 %). Five patients (83 %) in the PD group experienced POPF, and three patients (27 %) in the CS group experienced anastomotic fistula: one patient after re-implantation of the papilla in a jejunal patch during segmental resection of the D2 and the two other patients after primary closure of the duodenal defect during wedge resection of a D2 and D3 tumor. The median duration of hospital stay was shorter in patients of the CS group (12 days) when compared with patients of the PD group (42 days).

Pathological Findings

Pathological findings are listed in Table 3. The preoperative diagnosis of a duodenal GIST was correct in six patients (35 %). The median size of the tumor was 40 mm (range, 12–160). No differences were noted between groups according to tumor size and tumor location. However, patients in the PD group had more tumors located on the pancreatic

side of the duodenum. All tumors were resected with clear surgical margins (R0) and without rupture of the capsule. According to the Miettinen classification, five GISTs in the PD group (83 %) were considered to be at high risk of recurrence compared with three (27 %) in the CS group.

Survival

No patients were lost to follow-up. Median follow up was 34 months. Except for one patient who died postoperatively (PD group), all patients were alive at the censor date. Two patients developed recurrences (12 %): One patient in the PD group developed liver metastases 48 months after surgery and was treated medically, and one patient in the CS group developed a local recurrence 45 months after surgery and was treated by iterative CS. Median disease-free survival rates of the PD group and CS group were 29 and 36 months, respectively.

Discussion

GISTs are the most common mesenchymal tumors of the gastrointestinal tract. Although the surgical management for a GIST in the stomach or in the small intestine is well-described,^{10,11} the appropriate procedure for a duodenal GIST remains undetermined due to the following reasons: (a) duodenal GISTs are rare (less than 5 % of all such tumors),^{1,4,5} and (b) the duodenal location represents a surgical challenge due to important neighboring anatomical structures. Thus, duodenal GISTs are mostly described in the literature with case-reports, and, to our knowledge, we have reviewed only four surgical series comparing PD with a conservative approach^{5,13,15,16} (Table 4). Therefore, it remains difficult for a surgeon dealing with such a tumor to decide what type of surgery he has to perform. Thus, based on our own surgical experience, we propose to define the most appropriate modalities of surgical management for a duodenal GIST.

Our series showed that CS was safer than PD and allowed similar oncologic results.

Table 2 Comparison of surgical data and post-operative outcomes between patients treated by PD or CS

	Patients requiring transfusion (%)	8	(47)	4	(67)	4	(36)
	Mortality (%)	1	(6)	1	(17)	0	
	Morbidity (%)	10	(59)	6	(100)	4	(36)
	Clavien I–II (%)	4	(23)	2	(33)	2	(18)
	Clavien III–IV (%)	5	(29)	3	(50)	2	(18)
	POPF grade B/C (%)	8	(47)	5	(83)	3	(27)
POPF post-operative pancreatic fistula	Duration of hospital stay (days) (range)	14	(7–115)	42	(19–115)	12	(7–50)

Table 3 Comparison of pathological findings between patients treated by PD or CS

Characteristics	All patients		PD group		CS group	
Appropriate pre-operative diagnosis (%)	6	(35)	1	(17)	5	(45)
Size (mm) (range)	40	(12–160)	58	(22–140)	30	(12–160)
Location						
D1 (%)	1	(6)	0		1	(9)
D2 (%)	10	(59)	5	(83)	5	(45)
D3 (%)	3	(18)	0		3	(27)
D4 (%)	3	(18)	1	(17)	2	(18)
GISTs on the pancreatic side (%)	5	(29)	4	(67)	1	(9)
Miettinen high-risk tumors (%)	8	(47)	5	(83)	3	(27)
Number of recurrences (%)	2	(12)	1	(17)	1	(9)
Disease-free survival (months) (range)	34	(3–146)	29	(3–156)	36	(5–73)

Postoperative Courses

As expected, PD was associated with a longer operative time, a longer duration of hospital stay, and a higher rate of post-operative complications than CS. The rate of major post-operative complications (Clavien grade III/IV) seemed to be higher in the PD group than in the CS group (50 % versus 18 %, respectively). Moreover, we supposed that long-term quality of life might be better after CS than after

PD. Although mortality and morbidity rates have decreased considerably over the past several decades, PD remains a complex surgical procedure with high post-operative mortality (up to 16 %) and morbidity rates (up to 65 %) due to pancreatic anastomotic leakage in most cases.^{17–20} In terms of PD performed for a duodenal GIST, our results were consistent with the literature^{13–16} and suggested that, with regard to post-operative outcomes, conservative surgery is preferable to avoid procedure-related morbidity of PD and preserve the patient's quality of life.

Table 4 Outcomes of the main duodenal GIST series

Author	Cases	Surgery	Complication	Number of recurrences
Miettinen et al. ¹² (2003)	156	21 PD ^a 84 CS ^a	5 deaths in the entire population	49 in the entire population
Wienfield et al. ¹³ (2006)	8	5 PD 2 CS	1 death 0	1 1
Goh et al. ⁵ (2008)	14	7 PD 7 CS	3 minor 3 minor ^b 1 death	2 1
Chung et al. ¹⁴ (2010)	9	0 PD 9 CS	— 1 major 1 minor	— 0
Tien et al. ¹⁵ (2010)	25	9 PD 16 CS	3 minor 1 death 1 major 1 major	4 3
Buchs et al. ¹⁶ (2010)	7	2 PD 5 CS	0 0	2 0
Our series	17	6 PD 11 CS	2 minor 4 major 2 minor 2 major	1 1

Major Clavien grade $\geq$ III, minor Clavien grade <III

^a The exact type of surgery was unknown in 51 cases

^b The number of complications is calculated for 13 patients (seven GISTs and six other duodenal tumors)

Survival

In our series, all GISTs were resected with disease-free resection margins and without rupture of the capsule; thus, disease-free survival was similar in the CS group and PD group, and all patients were alive at the censor date. The prognosis of duodenal GISTs depends only on the tumor's potential for malignancy and the quality of the surgical resection (complete removal of the tumor with clear, 2-cm surgical margins and avoidance of tumor rupture, except when extracapsular GIST mobilization is possible).^{1,21} The tumor's potential for malignancy is based on the Miettinen scale.⁹ Tumors that exceed 5 cm and have an index greater than 5/50 HPF have an increased likelihood for local recurrence and metastatic spread. In our series, we noted that patients in the PD group were more frequently classified as having high-risk tumors. However, patients in the PD group did not have a worse prognosis. We could argue two interpretations:

- Those patients could have benefitted from a CS, or
- Those patients underwent an appropriate PD which permitted a free-margin resection; a CS would have resulted in an R1/R2 resection with impaired survival.

We did not have strong arguments for selecting the optimal procedure in such patients. In the literature, CS has been shown to have similar survival as PD.^{5,13,15,16}

Choosing the Procedure

Based on our findings, we propose to define a decision-making algorithm for the management of a duodenal GIST. Size and location of the tumor along the duodenal frame should not influence the choice of procedure (Table 2); thus, only the involvement of the pancreatic side was a determinant in the choice of a PD. However, one patient with a tumor involving the pancreatic side of the duodenum underwent a CS with an R0 margin; reconstruction was managed with re-implantation of the papilla in a Roux-en-Y duodenojejunostomy. Except in this isolated case, strongly influenced by both the surgeon's and center's experiences, PD should be the appropriate procedure in patients with GIST involving the pancreatic side of the duodenum. In fact, only the distance from the tumor to the ampulla has to be considered for the surgical decision. When the tumor is too close to the ampulla, the only way to achieve an R0-margin resection is to perform a PD.

Patients should be staged systematically with endo-ultrasonography and pancreatic MRI to assess (a) the precise location of the tumor in the duodenal frame (i.e., along or in front of the pancreatic side) and (b) the distance to the ampulla. Two situations:

A. *Patients not eligible for a CS:* An intraoperative pancreatic ultrasonography should be performed to precisely assess the distance between the tumor and the ampulla, or by opening the second portion of the duodenum. In recent years, studies on imatinib mesylate (IM, Glivec®, Novartis, Basel, Switzerland) have garnered interest regarding the treatment of unresectable or metastatic GISTs, demonstrating a significantly increased 2-year survival rate of 70 %.²² IM is also effective in an adjuvant setting for patients who have a significant risk of relapse.²³ Several studies have used IM in a neoadjuvant approach, demonstrating that IM decreases tumor size, allowing less extensive surgery to be performed for primarily unresectable tumors.²⁴ Thus, a neoadjuvant treatment might be envisaged for patients not eligible for a CS to downsize the tumor and spare the patients from a PD. However, there is currently no data in the literature to support this supposition. Moreover, it is unclear if the ampulla should be removed even if the downsizing permits a CS. The possibility of such a management has to be checked in a prospective study. Thus, based on our own experience and the literature, the patients for which the tumor is too close to the ampulla to achieve a R0 margin resection should benefit from a PD. In January 2012, we began a prospective evaluation of the neoadjuvant IM in patients with GIST involving the pancreatic side of the duodenum.

B. *Patients eligible for a CS:* Intraoperative pancreatic ultrasonography should be performed to help surgeons choose the appropriate procedure. When a CS is performed, extemporaneous histological analysis is needed to assess the resection margins. When the tumor is too close to the ampulla to achieve a R0 margin or when the resection margins are positive, a PD has to be performed.

Conclusion

CS was safe and provided similar oncologic outcomes as PD. CS should be the procedure of choice in patients with GIST that does not involve the pancreatic side of the duodenum. If a patient is ineligible for a CS according to preoperative staging or intraoperative ultrasonography (tumor too close to the ampulla to achieve a R0 margin), a PD has to be performed. The possibility of a neoadjuvant approach to avoid the procedure-related morbidity and poor long-term quality of life of PD has to be checked in a prospective setting.

Acknowledgments The authors gratefully acknowledge Doctor Olivier Turrini (Paoli-Calmettes Institute, Department of Oncologic Surgery) for his help during the preparation of this manuscript.

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