Clinical Science

Pancreas-sparing duodenectomy for gastrointestinal stromal tumor

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Abstract

BACKGROUND: Pancreas-sparing duodenectomy (PSD) is a promising alternative procedure to pancreaticoduodenectomy for the treatment of duodenal tumors with low-grade malignant behavior.

METHODS: Between March 2003 and September 2012, PSD was performed in 7 patients with a gastrointestinal stromal tumor (GIST) in the second (\(n = 5\)) or third (\(n = 2\)) portions of the duodenum. The short- and long-term outcomes of treatment were analyzed in all patients.

RESULTS: The median blood loss was 160 mL, and the median operative time was 315 minutes. No pancreatic leakage or perioperative mortality occurred. Surgical margins were negative in all cases. All patients were alive at the median follow-up time of 42 months after PSD. The recurrence-free 5-year survival rate was 53% in all patients. Hepatic metastases developed in 2 of the 5 patients with high- or intermediate-grade risks at the time of diagnosis. Hepatic resection was performed, and imatinib mesylate was administered in the 2 cases.

CONCLUSIONS: Good short- and long-term outcomes and surgical curability were observed in patients treated with PSD for duodenal GIST.

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Gastrointestinal stromal tumors (GISTs) are unique neoplasms that occur in the alimentary tract. GISTs frequently show expansive growth and rarely metastasize to the lymph nodes. In approximately 50% of cases, GISTs occur in the stomach; 30% occur in the small intestine, 5% in the colon and rectum, and 5% in the esophagus.\(^1\) GISTs in the small intestine occur in the duodenum in 12% to 18% of cases\(^2\) (ie, 3.6% to 5.4% of all GISTs arise in the duodenum). Surgical resection is recommended for the treatment of localized duodenal GISTs.\(^3\)

Pancreaticoduodenectomy (PD) remains a standard procedure for tumor resection not only in the pancreas but also in the duodenum.\(^3\) Despite advances in perioperative management and surgical techniques, postoperative complications, including pancreatic fistula after PD, still occur at an incidence of 30% to 50%.\(^5,6\) and the operative mortality

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after PD reported from high-volume hospitals ranges from 1% to 7.8%. Thus, less invasive organ-preserving surgery may be beneficial for patients with low-grade duodenal malignancies such as GISTs for which extensive resection is not required.

Pancreas-sparing duodenectomy (PSD) may be an attractive alternative procedure to PD for duodenal low-grade malignancies. Surgical indications of PSD can be divided into 3 categories: early-stage neoplasms, isolated duodenal neoplasms in high-risk patients, and duodenal involvement from adjacent organ malignancies. Although several authors have reported on the efficacy of PSD for various duodenal neoplasms, surgical outcomes of PSD for GISTs have never been summarized. The objective of the present study was to evaluate short- and long-term outcomes in 7 patients undergoing PSD for GISTs arising from the duodenum.

**Patients and Methods**

**Study population**

A review of the personal experiences of 1 of the authors (Y.S.) with GIST treatment and of patients with duodenal GISTs treated at 3 hospitals between the University of Tokyo Hospital, Cancer Institute Hospital of Japanese Foundation for Cancer Research, and National Cancer Center Hospital, Tokyo, Japan, between March 2003 and September 2012 was retrospectively analyzed. Patient records were examined for details of demographic characteristics, therapeutic procedures, complications after treatment, pathological findings, and postoperative long-term outcomes.

**Preoperative treatment**

Imatinib mesylate (400 mg/d for 8, 11, and 24 months) was administered preoperatively in 3 patients with locally advanced duodenal GISTs to reduce the tumor burden.

**Surgical procedures**

During resection of the second portion of the duodenum, 3 preservative measures were taken. First, the position of the major papilla was confirmed using careful palpation of the papilla or the tube inserted in the cystic duct after cholecystectomy. Second, during dissection of the duodenum from the pancreas, the pancreatic parenchyma was completely preserved to avoid postoperative pancreatic leakage. Because of the proximity of the pancreatic parenchyma to the minor papilla and its tight adherence to the duodenal wall, the muscle layer of the duodenum was occasionally exposed in the dissecting plane. The duct of Santorini was ligated and divided, but the major papilla was preserved in all cases. Third, after segmental resection of the second portion of the duodenum, the duodenal stump was closed, and Roux-en-Y reconstruction was performed to separate the alimentary root from the duodenal stump. After segmental resection of the third portion of the duodenum, end-to-side anastomosis between the residual duodenum and the proximal jejunum was performed.

After PSD, the resected specimens were examined pathologically. Risk stratification was determined using the following variables: maximum tumor diameter, mitotic count, and MIB-1 labeling index values according to the classification described by Fletcher et al.

**Postoperative follow-up**

Postoperative pancreatic fistula (POPF) and delayed gastric emptying (DGE) were graded according to the definition proposed by the International Study Group. Complications other than POPF and DGE were classified according to the criteria proposed by Clavien and Dindo. Only complications of grade 2 and above were recorded. Systemic follow-up included physical examination and computed tomographic scanning at 6-month intervals for up to 5 years after surgical resection. Since April 2012, postoperative adjuvant therapy with imatinib mesylate at 400 mg/d has been administered for histologically proven primary intermediate- and high-risk GISTs with macroscopic complete resection as outlined in a previous report. When the patient underwent the therapy with imatinib mesylate, any adverse events were recorded according to the National Cancer Institute Common Toxicity Criteria.

**Results**

**Characteristics of patients treated by pancreas-sparing duodenectomy**

PSD was performed in 7 patients with duodenal GISTs (3 men and 4 women; median age = 47 years; range 31 to 66 years) during the study period (Table 1). Neoadjuvant therapy using imatinib mesylate was administered in 3 patients (cases 3, 4, and 7). Significant tumor shrinkage was observed in 2 of these patients (95.8% [case 3] and 92.9% [case 4] tumor volume reduction). In the third patient (case 7), the administration of imatinib mesylate for 11 months at a local hospital had resulted in stable disease. Thereafter, the patient was referred to our institution where PSD was performed. Operative procedures included resection of the second (n = 5) and third (n = 2) portions of the duodenum. For 2 patients in whom resection of the second portion of the duodenum was performed, partial resection and primary closure (Fig. 1A) were used, and in 3 patients, segmental resection and Roux-en-Y reconstruction were performed (Fig. 1B). For patients in whom PSD was performed in the third portion of the duodenum, end-to-side anastomosis between the duodenum and the jejunal was selected (Fig. 1C).
Characteristics of operative procedures and short-term outcomes after pancreas-sparing duodenectomy

The median blood loss was 160 mL (range 100 to 865 mL), and the median operative time was 320 minutes (range 202 to 502 minutes) (Table 1). Among the 5 patients in whom surgery was performed in the second portion of the duodenum, the ducts of Santorini were ligated and resected in 3 patients. Of the 2 patients in whom surgery was performed in the third portion of the duodenum, 1 patient required papilloplasty without reconstruction of the major papilla. In all patients, the major papilla was preserved. Lymph nodes proximal to the duodenum were removed, but systematic nodal dissection around the pancreatic head was not performed. Regarding postoperative complications, central vein catheter infection (n = 1) and deep vein thrombosis (n = 1) were observed; however, no DGE or POPF occurred in any patient. No postoperative mortality was observed. The median duration of hospital stay was 14 days (range 11 to 30 days).

Pathological findings

The median maximal tumor diameter was 5.6 cm (range 3.0 to 9.0 cm). In 5 patients (71%), the size of the tumors was greater than 5 cm in diameter at surgical resection (Table 2). Mitotic counts varied from 0 to 18 per 50 high-power field (HPF) (median = 2/50 HPF), and 2 patients (29%) presented with greater than 10/50 HPF. MIB-1 labeling index values varied from 1% to 49% (median = 3%), and 2 patients (29%) presented with greater than or equal to 10%. As for the risk of aggressive tumor behavior, 16 2 cases (29%) were classified as low-grade, 3 cases (43%) as intermediate-grade, and 2 cases (29%) as high-grade at the time of surgical resection. In 1 patient, the risk stratification was downgraded after neoadjuvant therapy with imatinib mesylate from high-grade at the time of diagnosis to intermediate at surgical resection. Surgical margins were negative in all patients.

Long-term outcomes after pancreas-sparing duodenectomy

Long-term outcomes are summarized in Table 2. In the months since April 2012, PSD was performed in 2 patients who received postoperative imatinib mesylate (400 mg/d) as adjuvant chemotherapy (cases 6 and 7). The median follow-up duration was 42 months (range 2 to 72 months), and the median overall survival time was 42 months (range 2 to 72 months). All patients were alive during the follow-up period. The 3- and 5-year recurrence-free survival rates were both 53% (Fig. 2). Only 1 patient (case 3) sometimes takes proton pump inhibitor for mild heartburn. All the other patients have no late comorbidity such as biliary infection, pancreatitis, weight loss, or heartburn. None of them have degradation of quality of life. None of the 4 patients who underwent imatinib mesylate treatment has experienced grade 3 or 4 adverse events so far.

Two of the 5 patients with high- or intermediate-grade risks developed hepatic metastases. Hepatic resection was performed in 1 patient 6 months after surgical removal of the primary tumor, and imatinib mesylate was administered in the other patient to maintain stable disease for 21 months. Other 5 patients including 2 low-, 2 intermediate-, and 1 high-grade risk were alive with no evidence of recurrence or metastasis at the end of the follow-up period.

Comments

PSD for duodenal GISTs has been sporadically reported. However, the present report is the first to summarize the short- and long-term outcomes in patients treated by PSD for duodenal GISTs.

The incidence of nodal metastasis of GISTs is reported to be 0% to 3.4%.24–27 The National Comprehensive Cancer Network guidelines recommend curative resection and not extensive nodal dissection in cases of GISTs.3 In a retrospective surveillance study, Valadão et al28 showed that GIST lymph node metastasis was not related to poor survival.

The goal of surgery for GISTs is complete tumor resection with negative surgical margins.29 This goal was accomplished
in the 7 patients in whom PSD was performed in the present study. Johnston et al.30 speculated that the recurrence of duodenal GISTs was dependent on tumor biology rather than the surgical approach. In the 7 cases presented here, 2 patients with low-grade risk were alive with no evidence of recurrence or metastasis at the end of the follow-up period. Liver metastases developed in 2 of the 5 patients with high- or intermediate-grade risks at the time of diagnosis 6 and 21 months after PSD. These results suggest that the prognosis of patients with duodenal GISTs is largely determined by tumor biology, which can be estimated by tumor size, mitotic count, and labeling index values. Extensive surgery involving nodal dissection, such as that required for PD, may therefore be unnecessary in the treatment of duodenal GISTS. PSD may be widely applicable in cases of duodenal GISTs in which negative surgical margins can be obtained.

Figure 1  Operative procedures. (A) The tumor (black asterisk) located in the second portion of the duodenum was partially resected (dotted line, left), and primary closure of the duodenal wall was performed (right). (B) The tumor (black asterisk) located in the second portion of the duodenum was segmentally resected (left), and Roux-en-Y reconstruction was performed (right). The duct of Santorini was ligated (black arrowhead), and the stump of the duodenum was closed (black arrow). (C) The tumor (black asterisk) located in the third portion of the duodenum was segmentally resected (left), and end-to-side anastomosis between the residual duodenum and the proximal jejunum (right) was performed.
Duodenal GISTs frequently involve the second portion of the duodenum and less often the third, fourth, and first portions. Thus, the detection of duodenal GISTs depends greatly on tumor size, location, and the presence or absence of mucosal ulceration, which is associated with symptoms of pain and bleeding. Small duodenal GISTs not involving the papilla of Vater are amenable to limited resection. However, when the major papilla or pancreatic parenchyma must be sacrificed because of the invasion of a large tumor, conventional PD may be recommended to achieve adequate tumor clearance.

PSD with reimplantation of the major papilla is extremely technically demanding, and patients are at a higher risk for morbidity. The following conditions were required for performing PSD in the duodenal GIST patients in our case series: the tumors could not invade adjacent organs or metastasize to the lymph nodes, and the major papilla needed to be technically preserveable. Of the 7 patients in the present study, neoadjuvant chemotherapy using imatinib mesylate was administered in 3 patients, which was very effective to induce tumor shrinkage, especially in 2 patients. Thereafter, PSD was performed for preserving the major papilla and total pancreas. Imatinib mesylate is a selective inhibitor of certain protein tyrosine kinases and blocks the constitutive activity of KIT receptor tyrosine kinase in GISTs. Although Demetri et al reported that serious gastrointestinal and tumor hemorrhage occupied 5% in the patients with advanced GISTs after tumor degeneration caused by imatinib mesylate, the therapy was mostly well tolerated. Actually in the present study, none of the 4 patients who underwent imatinib mesylate has experienced grade 3 or 4 adverse events. Although tyrosine kinase inhibitors control tumor growth in over 80% of patients, complete are only rarely achieved, and surgical resection remains the only potentially curative therapy for GISTs. Most patients who initially respond to imatinib eventually acquire resistance via additional mutations in the KIT gene. Therefore, surgical extirpation is required after the antitumor agent succeeds in inducing tumor shrinkage. In addition, debulking surgery of tumor burden followed by additional imatinib may delay or prevent the development of resistant clones, leading to a prolonged time to disease progression.

In the present patient series, hepatic resection for liver metastasis of duodenal GISTs was performed in 1 patient 6 months after surgical removal of the primary tumor. This patient has experienced a recurrence-free survival time of 60 months without additional therapy. However, the value of surgical resection for liver metastases from GISTs is controversial. Many patients eventually died of recurrent disease even after complete resection of liver metastases before the administration of imatinib mesylate. Because of the availability of kinase inhibitors, surgical intervention followed by the administration of imatinib mesylate or sunitinib malate should be considered for the control of metastatic or recurrent GISTs if R0 resection is expected.

In reality, radical surgical removal is the only chance of long-term survival for GIST patients even in the era of effective new chemotherapeutic regimens. The development of multidisciplinary strategies including surgery and kinase inhibitors may result in an improvement in

| Table 2 Pathological findings of the tumor and long-term outcomes of the 7 patients |
|---|---|---|---|---|---|---|
| No. | Size (cm) | Mitotic count (/50 HPF) | MIB-1 labeling index (%) | Risk stratification* | Surgical margin | Recurrence | Survival period (mo) |
| 1 | 3.5 | 2 | 3 | Low | R0 | — | 72 |
| 2 | 3.0 | 0 | 1 | Low | R0 | — | 71 |
| 3 | 7.5 | 0 | 3 | High/intermediate | R0 | Liver | 65 |
| 4 | 5.6 | 18 | 49 | High | R0 | Liver | 42 |
| 5 | 9.0 | 12 | 20 | High | R0 | — | 17 |
| 6 | 7.4 | 2 | 1 | Intermediate | R0 | — | 2.5 |
| 7 | 5.2 | 0 | 1 | Intermediate | R0 | — | 2.0 |

Case 3 revealed a downgrade of risk stratification through neoadjuvant therapy from high grade at the time of diagnosis to intermediate grade at surgical resection.

HPF = high-power field.

*The risk stratification was determined according to the classification described by Fletcher et al.
prognostic outcomes in patients with GISTs. Less invasive organ-preserving surgery, such as PSD with R0, may also improve the efficacy of chemotherapeutic treatment, which will be beneficial for patients. In conclusion, PSD is a satisfactory alternative procedure to PD to achieve curative resection with adequate safety and minimal invasiveness. PSD led to a satisfactory long-term outcome in patients with duodenal GISTs.

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