# Medicine®

# Small amounts of tissue preserve pancreatic function
## Long-term follow-up study of middle-segment preserving pancreatectomy

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**Abstract**

Middle-segment preserving pancreatectomy (MPP) is a novel procedure for treating multifocal lesions of the pancreas while preserving pancreatic function. However, long-term pancreatic function after this procedure remains unclear.

The aims of this current study are to investigate short- and long-term outcomes, especially long-term pancreatic endocrine function, after MPP.

From September 2011 to December 2015, 7 patients underwent MPP in our institution, and 5 cases with long-term outcomes were further analyzed in a retrospective manner. Percentage of tissue preservation was calculated using computed tomography volumetry. Serum insulin and C-peptide levels after oral glucose challenge were evaluated in 5 patients. Beta-cell secreting function including modified homeostasis model assessment of beta-cell function (HOMA2-beta), area under the curve (AUC) for C-peptide, and C-peptide index were evaluated and compared with those after pancreaticoduodenectomy (PD) and total pancreatectomy. Exocrine function was assessed based on questionnaires.

Our case series included 3 women and 2 men, with median age of 50 (37–81) years. Four patients underwent pylorus-preserving PD together with distal pancreatectomy (DP), including 1 with spleen preserved. The remaining patient underwent Beger procedure and spleen-preserving DP. Median operation time and estimated intraoperative blood loss were 330 (250–615) min and 800 (400–5500) mL, respectively. Histological examination revealed 3 cases of metastatic lesion to the pancreas, 1 case of chronic pancreatitis, and 1 neuroendocrine tumor. Major postoperative complications included 3 cases of delayed gastric emptying and 2 cases of postoperative pancreatic fistula. Imaging studies showed that segments representing 18.2% to 39.5% of the pancreas with good blood supply had been preserved. With a median 35.0 months of follow-ups on pancreatic functions, only 1 patient developed new-onset diabetes mellitus of the 4 preoperatively euglycemic patients. Beta-cell function parameters in this group of patients were quite comparable to those after Whipple procedure, and seemed better than those after total pancreatectomy. No symptoms of hypoglycemia were identified in any patient, although half of the patients reported symptoms of exocrine insufficiency.

In conclusion, MPP is a feasible and effective procedure for middle-segment sparing multicentric lesions in the pancreas, and patients exhibit satisfied endocrine function after surgery.

**Abbreviations:** AUC = area under the curve, CPI = C-peptide index, CT = computed tomography, DFI = disease-free interval, DGE = delayed gastric emptying, D-J = duodenojejunostomy, DM = diabetes mellitus, DP = distal pancreatectomy, DPPHR = duodenum-preserving pancreatic head resection, H-J = hepatojejunosotomy, HOMA = homeostasis model assessment, IAT = islet autotransplantation, IFG = impaired fasting glucose, IGT = impaired glucose tolerance, IPMNs = intraductal papillary mucinous neoplasms, ISGPS = International Study Group of Pancreatic Surgery, MPP = middle-segment preserving pancreatectomy, NGT = nasogastric tube, OGTT = oral glucose tolerance test, PDA = pancreatic dorsal artery, PDAC = pancreatic ductal adenocarcinoma,

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## 1. Introduction

Many diseases can manifest as multiple lesions in the pancreas, including intraductal papillary mucinous neoplasms (IPMNs), multiple endocrine neoplasia syndrome-type I, von Hippel-Lindau (VHL) syndrome, metastatic tumors to the pancreas, and, sometimes, pancreatic ductal adenocarcinoma (PDAC).[1–3] Except for the nonsymptomatic multiple benign cystic lesions observed in conditions, such as VHL syndrome and branch type-IPMNs, most conditions warrant surgical resection.[4]

Total pancreatectomy (TP) is currently regarded as the standard surgical treatment for multiple lesions involving the entire pancreas.[5] However, the apancreatic status after TP leads to complex disorders of glucose metabolism and nutrition balance, greatly compromising postoperative quality of life of patients. One of the most serious consequences after TP is brittle diabetes, and when compared with type I and type II diabetes mellitus (DM), apancreatic patients are hypersensitive to exogenous insulin which can lead to life-threatening insentient hypoglycemia attacks.[5] Meanwhile, due to exocrine insufficiency, absorption of saccharides and lipids is compromised, and malnutrition as well as hepatopathies can develop after resection of the entire gland.[5] To improve the quality of life of patients after TP, endocrine replacement therapies, such as islet autotransplantation (IAT), have undergone rapid advancement in recent years. However, this technique is reserved for chronic pancreatitis and not for tumors; the long-term functioning of the transplanted islet remains an unsolved issue, meaning that 36% to 90% of patients rely on insulin injections after IAT.[6] On the other hand, data from large cohort studies show that TP might not be as safe as previously thought. In the United States, morbidity and mortality rates after TP remain as high as 28% to 47% and 2% to 8.5%, respectively.[7,8]

Since 1999, a new procedure termed middle-segment preserving pancreatectomy (MPP) has been described for the treatment of middle-segment sparing multifocal lesions in the pancreas.[9] The idea of this procedure is to combine right resection for head lesions and left resection for body-tail lesions, while preserving the pancreatic body segment with its blood supply from the pancreatic dorsal artery (PDA). Several rationales were proposed to support this novel procedure. First, compared with TP, this procedure provides the maximal possibility of preserving pancreas parenchyma; second, even in malignant cases, the combination of 2 radical resections can fulfill the oncological purpose; and third, it was reported that most endocrine function can be preserved with just over 20% of pancreatic tissue.[10] However, evidence in support of this function-preserving procedure remains insufficient; we therefore reviewed our initial experiences of MPP for different indications, with oncological outcomes and pancreatic function evaluated in long-term follow-up studies. The major objective of our present study is to verify if MPP could preserve pancreatic function, especially endocrine function, in long-term perspective.

## 2. Materials and methods

### 2.1. Patients and data collection

From September 2011 to December 2015, 7 cases of MPP were carried out at the Pancreas Center of the First Affiliated Hospital of Nanjing Medical University, which is one of the largest pancreatic centers in China. Written consent for surgery was obtained from each patient. Five cases were included in this paper with analysis of long-term oncological and functional results, while Case 6 with missing data of oral glucose tolerance test (OGTT) and Case 7 with short follow-up time were excluded. Medical records of the patients, including preoperative work-ups, intraoperative data, postoperative complications, and hospital stays, were prospectively collected and retrospectively analyzed. This study was approved by the local ethics committee.

### 2.2. Operative technique

After the abdominal cavity was explored and extrapancreatic systemic metastasis ruled out, Kocher maneuver was carried out to mobilize the "C" loop of the duodenum and the pancreatic head. Classic "tunnel dissection" was then performed and resection was accomplished in 2 parts, always starting with pancreatic head resection. The procedures utilized for head resection included pylorus-preserving pancreaticoduodenectomy (PPPD) and duodenum-preserving pancreatic head resection (DPPHR, Beger procedure). During PPPD, we routinely transected the duodenum 0.5 cm distal to the pylorus to ensure a good blood supply to the duodenal stump, while right gastric artery was ligated. For DPPHR, a rim of pancreatic tissue inside the "C" loop of the duodenum was carefully preserved to ensure a good blood supply to the duodenum and common bile duct. Distal resection was performed with or without splenic vessel preservation. The distal pancreatic stump was closed using 4-0 absorbable interrupted sutures, with the main pancreatic duct ligated independently. During MPP, preservation of the PDA, which often originates from the splenic artery and less frequently from the hepatic common artery or celiac trunk, should be ensured. Intraoperative sonography was utilized to exclude the potential remaining lesion in the middle segment for tumor cases. Reconstruction of the alimentary tract was performed as follows: pancreaticojejunostomy (P-J) was done in an end-to-side invagination fashion with continuous or interrupted absorbable stitches. A second layer of Lembert suture was optional. Hepatojejunosotomy (H-J) was also done in an end-to-side manner with continuous stitches. Duodenojejunostomy (D-J) was always performed in a continuous manner, both for inner layer and Lembert sutures. A nasogastric tube (NGT), placed deep into the afferent jejunal loop with its tip close to the P-J and H-J, was used as external decompression drainage for the afferent loop after surgery. A nasojejunal tube was placed into the efferent loop, with its end located 30 cm distal to the D-J. A patch of greater omentum was utilized to isolate P-J from the vessels.

### 2.3. Definition of complications

Definition and grading of postoperative complications, including postoperative pancreatic fistula (POPF) and postpancreatectomy hemorrhage, was based on consensus definitions from the International Study Group of Pancreatic Surgery (ISGPS).[11,12] Serving the purpose of a decompressor for the afferent loop, the NGT was usually removed on postoperative day (POD) 6 or 7.

## Table 1

**Baseline data.**

|  | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 |
|---|---|---|---|---|---|
| Sex | M | F | M | F | F |
| Age, y | 37 | 81 | 48 | 52 | 50 |
| Comorbidities | None | HT 20 y<br>BE 40 y | None | None | None |
| ASA grading | II | II | II | II | II |
| DM history | 8 y | None | None | None | None |
| Preop. FBG, mmol/L | 3.5* | 5.3 | 4.37 | 4.69 | 5.22 |
| Steatorrhea | None | None | None | None | None |

ASA = American Society of Anesthesiologists, BE = bronchiectasis, DM = diabetes mellitus, HT = hypertension, Preop. FBG = preoperative fasting blood glucose.
* Controlled by subcutaneous insulin injection.

An alternative definition of delayed gastric emptying (DGE) than the ISGPS recommendation, which defines DGE as removal of the NGT after POD 10 or reinsertion of an NGT after POD 10, was therefore utilized.[13,14] The definition of DM was in accordance with World Health Organization guidelines.[15]

### 2.4. Follow-up and pancreatic function tests

All patients were followed up either by outpatient service visits or telephone interview. With the exception of routine examinations, clinical symptoms related to DM and exocrine insufficiency were investigated and computed tomography (CT) scans were also offered. Preservation ratio after MPP was calculated with CT volumetry (postsurgical pancreatic remnant volume divided by presurgical nonlesion pancreatic volume) on transverse sections with 5 mm slices in the portal vein phase with the best delineation observed around the parenchyma, as manually determined by a senior radiologist. In order to evaluate the endocrine function of the pancreas, a 75 g OGTT was offered to each patient during follow-up visits. Blood samples were collected for all participants at times 0, 30, 60, 120, and 180 min during the OGTT to measure glucose, insulin, and C-peptide levels. Beta-cell secretion was estimated by a modified homeostasis model assessment of beta-cell function (HOMA2-beta),[16] AUC for C-peptide,[17] and C-peptide index (CPI).[18] HOMA2-beta was evaluated using HOMA calculator software developed by the University of Oxford (http://www.dtu.ox.ac.uk/homacalculator/), AUC for C-peptide was calculated for the initial 120 min of the OGTT, and CPI was defined as the ratio of fasting C-peptide (mmol/L) to fasting plasma glucose (mmol/L). Exocrine pancreatic function was followed-up with evaluation on related symptoms. We retrospectively reviewed the follow-up studies after pancreaticoduodenectomy (PD) and TP, OGTT tests have been carried out in 11 consecutive PDs and 2 TPs among the total 348 PD cases and 2 TP cases during the same period for other research purposes. Endocrine function of patients after MPP was compared to those of patients after PD and TP.

### 2.5. Statistical method

Mann–Whitney U test was used to compare endocrine indices including HOMA2-beta, AUC for C-peptide, and CPI between every 2 groups of patients after TP, MPP, or PD. A P value <0.05 was considered as statistically significant.

## 3. Results

### 3.1. Baseline data

Three female and 2 male patients were included in this study. The median age was 50 years, with the oldest and youngest of 81 and

37 years, respectively (Table 1). Case 2 had a history of hypertension for 20 years and bronchiectasis for 40 years, while the remaining patients had no major comorbidities. All patients were classified as American Society of Anesthesiologists grade II. Case 1 was the only patient with a history of DM before surgery (8 years), but had well-controlled glucose levels between 3.5 and 12.2 mmol/L with subcutaneous insulin injection (28 U/d) upon admission. All other patients had no history of DM and their fasting glucose levels were between 4.37 and 5.3 mmol/L (Table 1). No patient took enzyme supplements or reported symptoms related to pancreatic exocrine insufficiency, such as steatorrhea. Case 3 had a history of cigarette smoking.

### 3.2. Diagnosis and indication for surgery

Three of the 5 patients (Cases 2–4) had a previous history of some type of tumor, including 1 case of renal clear cell carcinoma, 1 case of dermatofibrosarcoma protuberans (DFSP) in the shoulder, and 1 case of bilateral adrenal pheochromocytoma, respectively (Table 2). All 3 patients had received curative resection for the primary lesions. Considering the above history, together with the CT findings, preoperative diagnoses of these patients were multiple pancreatic metastases from previous malignancies (Fig. 1; Table 2). The remaining 2 cases were diagnosed as chronic pancreatitis with pancreatic duct stones and a multiple neuroendocrine tumor, based on clinical manifestations, laboratory, and imaging studies (Fig. 1; Table 2). Preoperative imaging studies showed that, in all cases, both the pancreatic head and tail regions were involved, with a body segment free of disease (Fig. 1). Extrapancreatic lesions were observed in 2 cases: case 3 had a metastatic lesion in the right lung and case 4 had recurrence in a previous surgical site of left adrenalectomy.

### 3.3. Intraoperative data and postoperative pathology

Curative surgery with standard lymphadenectomy was performed for patients with malignant diagnosis (cases 3 and 4 received additional resection for extrapancreatic lesions metachronously and synchronously) (Table 2). PPPD or DPPHR was performed for various pancreatic head lesions as appropriate. Spleen preservation was considered during left pancreatectomy for selected cases, based on the nature of the disease and lesion location (see details in Table 2). Operation time varied from 250 to 615 min (median: 330 min). Intraoperative estimated blood loss ranged from 400 to 5500 mL, while 2 to 18 U of packed red blood cell were transfused. As a result of surgical adhesions and recurrence of tumor in a previous surgical site, surgery for case 4

**Table 2**

**Surgical indications and intraoperative data.**

| | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 |
|---|---|---|---|---|---|
| Related history | CP; Partington procedure (4 y) | RCC; left nephrectomy (18 y) | Shoulder DFSP; local resection (2 y) | Adrenal PCC; bilateral adrenalectomy (R/L: 28/38 y) | None |
| Lesions on imaging studies | | | | | |
| Characteristics | Multiple duct stones, atrophic parenchyma | Mass with uneven enhancement | Roundish hypodensity mass with mild enhancement | Mass with strong enhancement | Hypodensity mass with calcification |
| Location | Pancreatic head and tail | Duodenum and pancreatic tail | Pancreatic head and body* | Pancreatic head and tail† | Pancreatic uncinate and tail |
| Max diameter, cm | — | 2.5 and 3.9 | Around 1.5 | 1.5–3.5 | 1.5–3.5 |
| Preoperative diagnosis | CP | Metastatic RCC | Metastatic DFSP | Metastatic PCC | PNET |
| Procedures‡ | | | | | |
| Proximal | Beger procedure | PPPD | PPPD | PPPD | PPPD |
| Distal | SPDP | DP | DP | DP | SPDP |
| Operation time, min | 370 | 250 | 285 | 615 | 330 |
| Intraoperative blood loss, mL | 1200 | 400 | 600 | 5500 | 800 |
| RBC transfusion, U | 4 | 2 | 4 | 18 | 4 |

CP = chronic pancreatitis, DFSP = dermatofibrosarcoma protuberans, DP = distal pancreatectomy, PCC = pheochromocytoma, PNET = pancreatic neuroendocrine tumor, PPPD = pylorus-preserving pancreaticoduodenectomy, RBC = red blood cell, RCC = renal cell carcinoma, SPDP = spleen-preserving distal pancreatectomy.

* Chest X-ray and thoracic computed tomography scan in case 3 showed a mass in the right lung, indicating a possible coexisting pulmonary metastasis.

† Recurrence was noticed in previous location of left adrenal on preoperative computed tomography.

‡ Case 3 underwent pulmonary lobectomy 3 months after pancreatectomy, while case 4 underwent a synchronous resection for recurrence of malignant pheochromocytoma at the original surgical site on the left.

was more complex, with the longest operation time and largest quantity of blood loss. Histological examination confirmed all preoperative diagnoses. Tumor diameter varied from 0.7 to 5 cm. All transection margins were free of malignancies, and all lymph nodes were free of metastasis (positive lymph nodes/total lymph nodes examined were 0/1, 0/1, 0/2, and 0/1 for cases 2, 3, 4, and 5).

### 3.4. Postoperative complications

DGE and POPF had the highest incidence rate (60% and 40%, respectively) in all postoperative complications (Table 3). All patients with DGE were successfully managed with conservative treatment, including fasting, gastric decompression, antacids, prokinetics, nutritional support and maintaining balance of water, and electrolyte. According to the ISGPS definition, POPF cases were all classified as grade B (Table 3). All cases were

conservatively managed, with drainage, antibiotics, and supportive treatments. Readmission happened in case 1 for epigastric pain and fever, 1 month after surgery. A liver abscess was discovered by ultrasound and CT and was successfully treated by CT-guided percutaneous drainage. No hemorrhage, biliary leakage, wound infection, wound dehiscence, or venous thromboembolism was observed. Ninety-day mortality was nil. Postoperative stay ranged from 21 to 60 days (Table 3).

### 3.5. Follow-up studies

Postoperative CT examinations showed that body segments were well preserved with good blood supply in all 5 patients, indicated by the marked enhancement effect of the remnant pancreas, while no signs of inflammation or necrosis were observed (Fig. 2). CT volumetry was carried out to estimate preserved pancreas parenchyma volume after surgery, with preservation of 18.2%
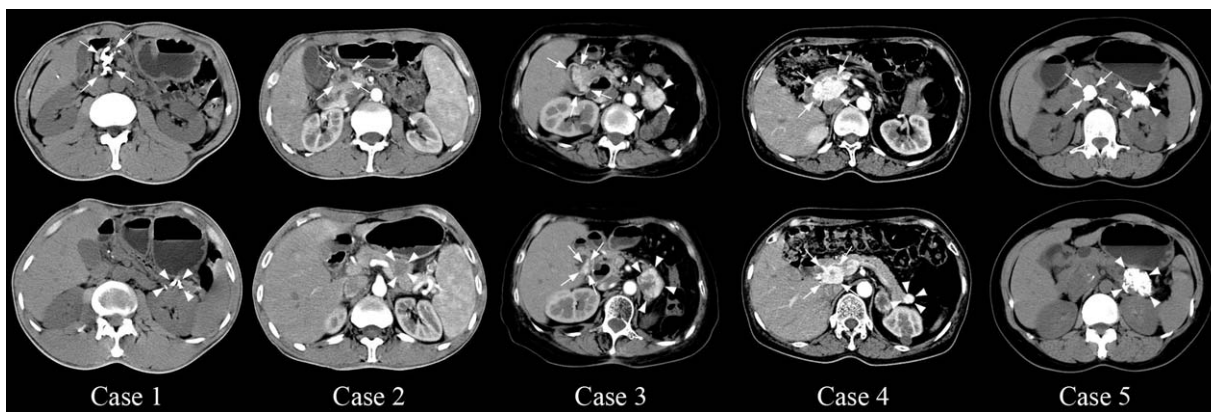


**Figure 1.** Preoperative abdominal CT scans. Lesions in head and tail portion of the pancreas were shown in the picture, with arrows for head lesions and arrowheads for tail ones. For improved identification of lesions, different phases of CT scanning are shown for different lesions (plain scan for cases 1 and 5, arterial phase for cases 2–4). CT = computed tomography.

**Table 3**

**Postoperative courses and complications.**

|  | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 |
|---|---|---|---|---|---|
| Complications |  |  |  |  |  |
| POPF | B | B | — | — | — |
| DGE | — | Yes | Yes | — | Yes |
| Others | — | — | — | Pleural effusion | — |
| Postoperative stay, d | 21 | 52 | 21 | 60 | 23 |
| Readmission | Liver abscess | — | — | — | — |

DGE = delayed gastric emptying, POPF = postoperative pancreatic fistula.

to 39.5% (18.4%, 39.5%, 38.9%, 35.8%, and 18.2%, respectively) of total volume of pancreas observed after MPP (Fig. 2). Average CT values of the remaining pancreas parenchyma at the portal venous phase were also measured for all patients, and varied between 60.1 and 103.4 HU (60.1, 94.8, 103.4, 92.5, and 94.0 HU, respectively).

After a median follow-up of 39.2 months, 2 patients died of malignancy progression at 8.7 (case 3) and 41.3 (case 2) months after surgery, due to systemic metastases. The remaining 2 patients with a diagnosis of malignancy were alive and free from recurrence or metastasis during the follow-up studies. For case 1, with chronic pancreatitis and severe abdominal pain after Partington procedure due to multiple stones and calcifications in the pancreas, symptoms were obviously relieved after MPP.

OGTTs (75 g) were carried out to evaluate the glucose metabolic status of 5 patients at 7.1 to 48.0 months (median: 35.0 months) after MPP (Table 4). Among the 4 cases without a previous history of diabetes, only 1 patient (case 2) had developed new-onset of DM (25%). For the remaining 3 patients, OGTTs

showed a normal glucose metabolic status in case 4, impaired glucose tolerance (IGT) in case 3, and impaired fasting glucose (IFG) in case 5 (Table 4). Case 1 reported slightly increased insulin usage after MPP (28–36 U/d), while case 2 started to receive a low dosage insulin injection for glucose control after surgery, and reported a total usage of 14 U/d at the last follow-up. Both patients receiving insulin injections had stable blood glucose levels and did not report any signs of hypoglycemic attack.

In order to further evaluate the endocrine function of preserved pancreatic tissue, we measured serum insulin and C-peptide levels after OGTT (Fig. 3A–C). Insulin levels varied from 0.60 to 16.10 mIU/L for the base value and 4.9 to 35.5 mIU/L for the peak value, while C-peptide ranged from 47.9 to 445 pmol/L and 282 to 2185 pmol/L for base and peak values, respectively. Peak time was 30 to 120 and 60 to 180 min, while the ratio of peak/base value ranged from 1.3 to 57.3 and 2.9 to 10.6 for insulin and C-peptide release, respectively. Cases 1 and 2 showed a peakless release curve at a low level, which was in accordance with their diabetic status. Case 4 showed a delayed peak (peak time 120
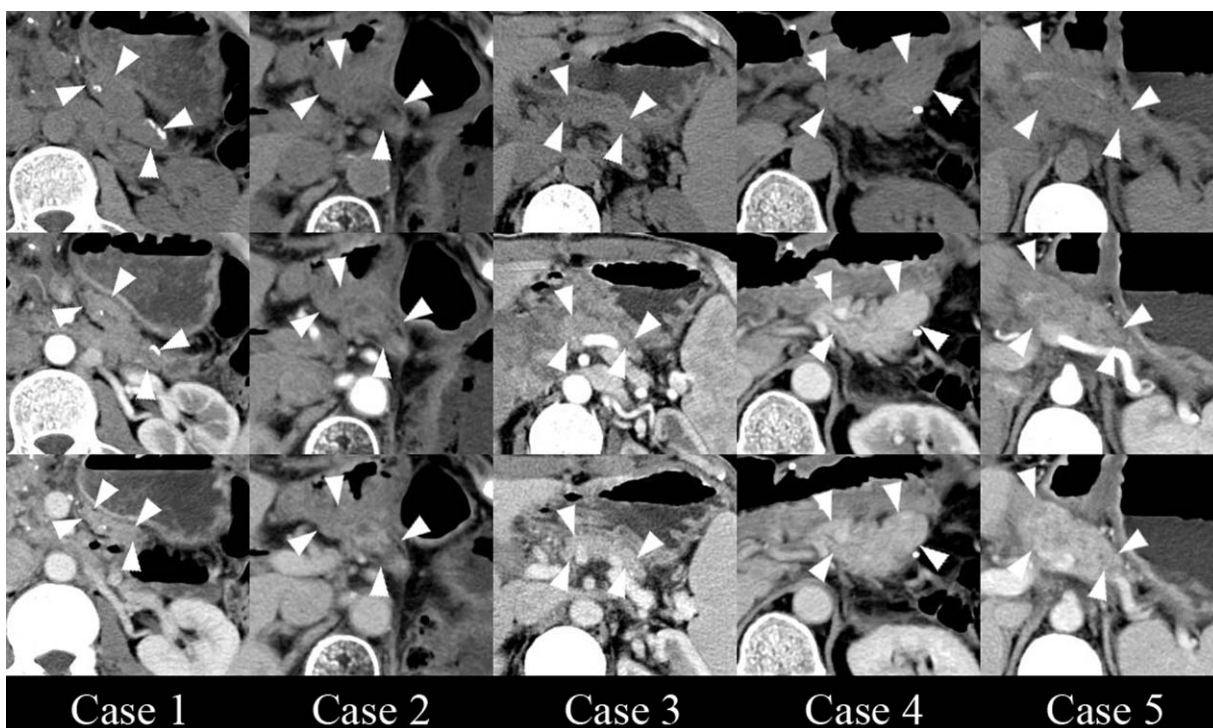


**Figure 2.** Postoperative follow-up imaging studies. CT showed that the middle segments of pancreas were well preserved in all cases without inflammation or necrosis (area indicated by arrowheads). CT volumetry showed a preservation of 18.4%, 39.5%, 38.9%, 35.8%, and 18.2% of total pancreatic volume in the 5 cases, respectively, while average CT values of the remaining pancreas parenchyma at the portal venous phase were 60.1 HU, 94.8 HU, 103.4 HU, 92.5 HU, and 94.0 HU, respectively. CT = computed tomography.

### Table 4

**Postoperative pancreatic endocrine and exocrine function after MPP.**

|  | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 |
|---|---|---|---|---|---|
| Follow-up time on functions, mo | 48.0 | 35.0 | 7.1 | 15.6 | 39.2 |
| Endocrine function |  |  |  |  |  |
|   Preop. FBG, mmol/L | 3.5[*] | 5.30 | 4.37 | 4.69 | 5.22 |
|   Postop. FBG, mmol/L | 8.17 | 7.4 | 5.42 | 5.54 | 6.33 |
|   Postop. OGTT 2 h, mmol/L | 21.9 | 13.38 | 9.65 | 4.01 | 5.75 |
|   Insulin usage, per d | 36 U | 14 U | None | None | None |
|   Status | DM | DM | IGT | Normal | IFG |
| Exocrine function |  |  |  |  |  |
|   Steatorrhea after fatty food | Yes | Yes | No | No | Yes |
|   Enzyme supplements, mg pancrelipase[†]/d | 900 | 900 | 0 | 0 | 450 |

DM = diabetes mellitus, FBG = fasting blood glucose, IFG = impaired fasting glucose, IGT = impaired glucose tolerance, MPP = middle-segment preserving pancreatectomy, OGTT = oral glucose tolerance test, postop. = postoperative, preop. = preoperative.

[*] Controlled with insulin injection.

[†] 150 mg pancrelipase contained 10,000 U lipase, 8000 U amylase, and 600 U proteinase.

min) release curve with a slightly lower peak/base ratio. Cases 3 and 5 had a normal release curve (Table 4; Fig. 3A–C). Beta-cell function was further evaluated with HOMA2-beta (cp), AUC for C-peptide and CPI, and was compared to values measured after TP or PD. Results showed that insulin secretion was at the lowest level after TP, and MPP seemed to have a better endocrine function in comparison to TP with marginal trends toward significance in 2 of 3 indices ($P$ values were 0.121, 0.053, and 0.053 for HOMA2-beta (cp), AUC for C-peptide, and CPI, respectively) (Fig. 3D–F). MPP and PD were quite similar in terms of preservation of beta-cell function ($P$ values were 0.234, 0.610, and 0.126), while unsurprisingly, the most significant difference existed between PD and TP (all 3 $P$ values were 0.030) (Fig. 3D–F).

Pancreatic exocrine function was followed-up, mainly based on patient self-reported questionnaires. Three of the 5 patients reported symptoms of steatorrhea after a fatty diet and relied on enzyme supplementation with a dosage of 450 to 900 mg pancrelipase per day (150 mg pancrelipase contained 10,000 U lipase, 8000 U amylase, and 600 U proteinase). The remaining 2 patients did not report any symptoms related to exocrine insufficiency (Table 4).

## 4. Discussion

Since the first case of staged MPP reported by Siassi et al[9] in a patient with multicentric pancreatic adenocarcinoma, 25 cases (4 two-stage, 21 one-stage) of this procedure have been reported to
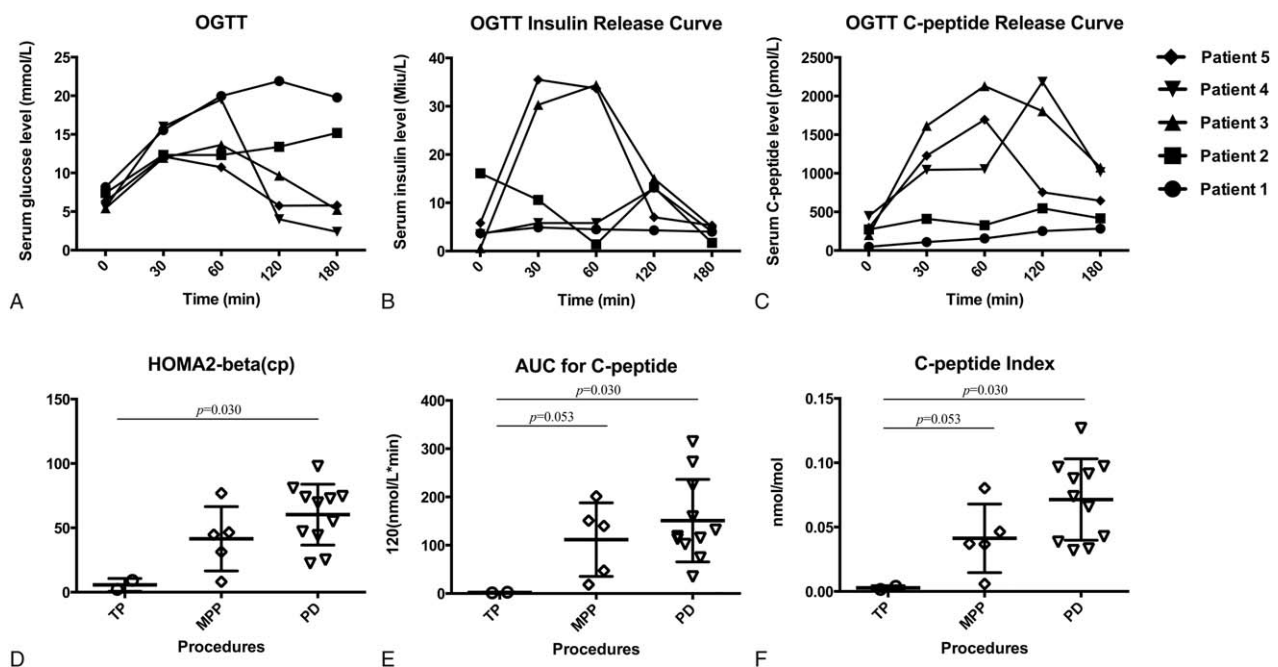


**Figure 3.** Pancreatic endocrine function including OGTT and beta-cell function tests during long-term follow-up studies. (A) OGTT; (B) OGTT insulin release curve; (C) OGTT C-peptide release curve; (D–F) comparison of beta-cell function parameters including HOMA2-Beta (cp), AUC for C-peptide and C-peptide index between patients after TP, MPP, and PD. AUC = area under the curve, HOMA2-beta = modified homeostasis model assessment of beta-cell function, MPP = middle-segment preserving pancreatectomy, OGTT = oral glucose tolerance test, PD = pancreaticoduodenectomy, TP = total pancreatectomy.

date.[9,19–32] However, most papers were case reports of small numbers of patients, with limited follow-up data on long-term pancreatic function. To our knowledge, our report of 7 cases of 1-stage MPP is the largest case series in the current literature, and the first to additionally present long-term endocrine follow-up data in 5 patients.

Indications for MPP are pancreatic body-sparing multifocal disease, including PDAC,[9,20] IPMNs,[24,32] neuroendocrine tumors (PNETs),[21,31] and metastatic tumors of the pancreas with a low-grade malignant nature.[23,29,30] In our current series, the major indications were metastatic tumors of the pancreas, including renal cell carcinoma (RCC), DFSP, and pheochromocytoma. The most common origin of pancreatic metastatic tumor reported in the literature is RCC; others include breast cancer, lung cancer, colonic cancer, and melanoma.[33] Currently, there is no high-level evidence available to define the role of surgical resection in treating metastatic lesions of the pancreas. However, several factors have been reported to predict prognosis and guide reoperation after primary tumor resection, including differentiation grade of the tumor, solitary versus systemic lesions, and disease-free interval (DFI) before the emergence of metastatic lesions.[33,34] In our cases, DFI of the tumors ranged from 2 to 38 years, and additional organs outside of the pancreaticoduodenal region were involved in 2 cases. Case 3 unexpectedly developed an early systemic recurrence and died at only 8.7 months after aggressive surgical treatment. However, this is in accordance with biological behavior after fibrosarcomatous changes in metastatic lesions in this patient, which is a microscopic description related to both high local recurrence rate (73–89%) and high metastasis rate (14–33%).[35] Thus, systemic treatment based on a multidisciplinary therapeutic strategy instead of surgery-first modality should be scheduled for such patients in the future. The remaining 2 metastatic cases with longer DFI and better differentiation showed much better responses to MPP. Multicentric low-grade or borderline malignancies are also good indications for MPP as the procedure is a combination of 2 radical pancreatectomies; thus, the requirements for standard lymphadenectomy could be theoretically fulfilled. However, 1 potential drawback of this study was the unsatisfied report of lymph node status in histology: only a total of 1 to 2 lymph nodes were examined for malignant cases, which would possibly cause false negative in reporting metastasis in lymph nodes. However, no lymphatic recurrence occurred in our cohort during long-term follow-up studies suggested that the lymphadenectomies in MPPs we performed were sufficient in terms of oncological purpose for the malignant cases.

The advantage of this procedure is that small amounts of normal pancreatic tissue are preserved to the maximum extent, with the intention of maintaining some part of endocrine and exocrine pancreatic function. It has been reported that only the resection of more than 80% of the pancreas can lead to compromised pancreatic endocrine function,[10] while for maintaining exocrine function, around 24 mL of tissue is required.[36] Our postoperative follow-up imaging studies showed that 18.2% to 39.5% of pancreatic parenchyma was preserved in our cases, and pancreatic remnants maintained a good blood supply as indicated by their robust enhancement effect after contrast injection. Accordingly, only 1 case of new-onset DM was reported in the 4 preoperatively euglycemic patients (25%), whose blood sugar was well controlled by 14 U/d of subcutaneous insulin injection. The remaining cases included 1 case of IGT and 1 case of IFG after surgery. Case 1, with a diagnosis of DM preoperatively, reported increased insulin

dosage from 28 to 36 U/d at 48 months postsurgical follow-up. OGTT-insulin/C-peptide release curves showed that 2 patients (cases 1 and 2) had peakless curves with low insulin/C-peptide levels, indicating insufficient release of insulin and significantly impaired islet function, in accordance with their clinical presentation. We further evaluated beta-cell function in our patient cohort using HOMA2-beta, AUC for C-peptide, and CPI, and all the parameters showed a fairly comparable beta-cell function to those measured after Whipple procedure, and seemed better than those after TP. Furthermore, neither patient receiving insulin injection reported symptoms related to hypoglycemic attacks during the follow-up period, a finding we believed to be related to the preservation of glucagon-secreting alpha-cells and could potentially improve long-term prognosis of the patients after surgery. We also investigated exocrine function of patients during follow-up visits and observed signs of insufficient exocrine function and enzyme supplement in 3 out of 5 patients.

Considering the increased extent of surgery, preservation of the middle segment of the pancreas can increase the chance of complications, especially POPF, compared with PD or TP. To date, the average complication rate after MPP reported in the literature is around 40%. In our cases, the most frequent complications were DGE (60%) and POPF (40%). All patients with POPF were graded as B according to the ISGPS definition and recovered well after conservative treatment. One of the reasons why MPP caused such a high rate of POPF in our series was likely due to the creation of 2 resection margins during surgery, similar to central pancreatectomy. Although we emphasized to preserve the dorsal pancreatic artery, potential ischemia of the pancreatic remnant could be another important reason for the high incidence of POPF observed after MPP. The other major complication in our series was DGE, which may potentially be related to the high rate of POPF after surgery. The other important factor related to DGE was the use of an NGT as an afferent loop decompressor to decrease POPF, which we routinely kept in place for 6 to 7 days after surgery and which may have promoted the diagnosis of DGE. No postpancreatectomy hemorrhage was observed in our current patient cohort. Other complications included liver abscess in case 1, 1 month after surgery, resulting in readmission and treatment with CT-guided percutaneous drainage. We consider the relatively high rate of complications to be related to the procedure per se, and less to a technical issue, given that the clinically relevant POPF rate according to the ISGPS definition after PD in our team during the same period was 12.6% (data not published).

Because of the rare surgical indications, small case number is the major limitation of studies on MPP. However, with a total of 7 cases, our present study is one of the largest case series of MPP that had been published so far. Due to the limited data on the postoperative long-term pancreatic function in patients after MPP, PD, and TP, our analysis cannot reach a satisfied statistical power, even though, the results suggested a preservation of pancreatic endocrine and exocrine function in patients after MPP. The other major limitation of this study was that we only followed-up the exocrine function of patients after MPP based on symptoms, and further studies with more objective tests for exocrine function are needed.

In summary, MPP is a function-preserving procedure with satisfactory feasibility and effectiveness; however, it can lead to a considerable increase in the incidence of postoperative complications. The most notable advantage of this procedure is the preservation of pancreatic function to the maximum extent with a small amount of pancreatic tissue, thus might avoiding the high

morbidity and mortality attributed to apancreatic status after TP. Although this procedure is designed for all cases with multifocal lesions involving almost the entire pancreas but sparing the middle segment, patients who can tolerate potential complications and have a relatively good prognosis (e.g., long DFI for metastatic malignancies) would most likely benefit from this procedure.

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