

**Original Article**

**Surgical Strategy for Main Pancreatic Duct-Type Intraductal  
Papillary Mucinous Neoplasm of the Pancreas**

**Running title: Surgical strategy for main duct IPMN.**

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**ABSTRACT**

**BACKGROUND/AIMS:** Although surgical resection is recommended for all main duct-type intraductal papillary mucinous neoplasms (IPMNs), controversies remain over the precise surgical strategy that should be adopted. This study thus aimed to investigate the appropriate surgical strategy for main duct IPMNs.

**METHODOLOGY:** We retrospectively evaluated 46 patients with main duct-type IPMNs who underwent surgical resection at a single center between 1991 and 2010.

**RESULTS:** Only 1 patient underwent total pancreatectomy (TP). Three patients underwent repeated pancreatectomy: TP was performed after distal pancreatectomy (DP) in 2 of these patients and after pylorus-preserving pancreaticoduodenectomy (PPPD) in the remaining patient. The recurrent histology indicated minimally invasive carcinoma in all 3 of these patients. Among the 6 patients who died in the present study, no deaths occurred due to local recurrence of the remnant pancreas.

**CONCLUSIONS:** Total pancreatectomy should be considered very selectively in the presence of a malignant lesion spreading to the whole pancreas.

**Key words:** Main pancreatic duct type; Intraductal papillary mucinous neoplasm; Total pancreatectomy.

## **Introduction**

Recently, many benign and low-grade malignant pancreatic lesions, including intraductal papillary-mucinous neoplasms (IPMNs), have been detected as a result of improvements in diagnostic modalities. IPMNs have been defined and classified by the World Health Organization and distinguished from other mucin-producing cystic neoplasms of the pancreas.<sup>1</sup> IPMNs are characterized by the dilatation of the pancreatic ducts, mucin hypersecretion and the papillary epithelial component.<sup>2-4</sup> IPMNs are classified into 2 types according to their site of occurrence: the main duct-type and branch duct-type.<sup>2</sup> IPMNs have a wide spectrum of histological findings, ranging from hyperplasia to adenoma to noninvasive or invasive carcinoma.<sup>5</sup> In addition, IPMNs show a more favorable prognosis than typical pancreatic carcinomas.<sup>6</sup>

The rate of the malignancy of the branch duct IPMNs is low, whereas main duct IPMNs are frequently malignant.<sup>7-9</sup> The average frequency of malignancy in main duct IPMNs based on several reports is 70%.<sup>10</sup> Therefore, the current treatment recommendation is that all main duct IPMNs should be considered candidates for resection.<sup>2, 3</sup> On the other hand, several controversies remain over

the surgical strategy for main pancreatic duct-type IPMNs. Several reports have demonstrated that total pancreatectomy (TP) should be selected to achieve a full cure in patients with main duct IPMNs in which the main pancreatic duct shows diffuse dilatation to the whole pancreas.<sup>11, 12</sup> However, the dilatation of the main pancreatic duct to the whole pancreas might occur through the production of large amounts of mucin and/or associated chronic pancreatitis.<sup>13</sup> On the other hand, care must be taken when adapting the TP for IPMN, since TP causes severe and permanent pancreatic endocrine/exocrine insufficiency, and IPMNs are slow-growing and have a relatively favorable prognosis even when malignant.<sup>14, 15</sup> In this study, we evaluated the surgical strategy for the main duct-type IPMN of the pancreas.

## **Patients and methods**

Between 1991 and 2010, 46 patients with main duct-type IPMNs underwent surgical treatment at the Department of Surgery, Nagasaki University Hospital. Main duct IPMN was defined by imaging studies including ultrasonography (US), computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP), and endoscopic retrograde cholangiopancreatography (ERCP), according to the international consensus guidelines.<sup>2</sup> In brief, main duct IPMNs showed a dilated main duct with a minimum width of 5 mm and contained mucus based on imaging with ERCP. IPMN with cystic dilatation of the branch ducts was included when there was more than 10-mm dilatation of a main duct, which corresponded to predominantly main duct-type IPMN.<sup>2</sup>

A retrospective review of clinical data was performed, including demographics, operative characteristics, and postoperative follow-up. Postoperative follow-up was based on clinical, radiologic and laboratory assessment at least 6 months after surgery. The preoperative data obtained included age, gender, results of the oral glucose tolerance test (OGTT), hemoglobin A1c (HbA1c) levels, and *N*-benzoyl-tyrosyl-*p*-aminobenzoic acid

(BT-PABA) test results. An abnormal glycemic response to the OGTT was defined according to the criteria proposed by the World Health Organization study group on diabetes mellitus.<sup>16</sup> Intraoperative data obtained included the type of pancreatic resection, diameter of the main pancreatic duct, mural nodule, and histology.

All patients underwent surgery and had a confirmed pathological diagnosis according to the World Health Organization criteria and the Classification of pancreatic carcinoma proposed by the Japan Pancreatic Society.<sup>17</sup> Intraoperative frozen section analysis of the pancreas cut surface was performed routinely. When the resection margin was diagnosed as positive, an additional pancreatic resection of the remnant pancreas was carried out to achieve a negative margin.

## **Results**

### **Clinical characteristics**

The characteristics of all patients in this study are listed in Table 1. The mean age was 68.5 years. There were 29 males and 17 females. Regarding clinical symptoms, 29 patients were asymptomatic and 17 patients had symptoms including abdominal pain (n=12), jaundice (n=2), loss of weight (n=2), and back pain (n=1). Results of the OGTTT were normal in 26 patients, and indicated impairment or diabetes in 20 patients. The mean HbA1c level was 6.3%, and the mean BT-PABA test score was 57.1%.

### **Operative characteristics**

The operative characteristics are listed in Table 2. Fifteen patients underwent pylorus-preserving pancreaticoduodenectomy (PPPD), and 6 patients underwent laparoscopic PPPD (Lap-PPPD). Six patients underwent distal pancreatectomy (DP), and 2 patients underwent laparoscopic DP (Lap-DP). We performed pancreaticoduodenectomy (PD) in 5 patients and total pancreatectomy (TP) in 1 patient. Limited resections of the pancreas were performed in 11 patients, and consisted of pancreatic head resection with segmental duodenectomy (PHRSD) in

5 patients, duodenum-preserving pancreatic head resection (DPPHR) in 3 patients, and middle pancreatectomy (MP) in 3 patients. The maximum diameter of the main pancreatic duct was < 10 mm in 22 patients, and was  $\geq 10$  mm in 24 patients. In 20 patients, no mural nodule was detected, while a mural nodule of < 10 mm was detected in 9 patients, and a mural nodule of  $\geq 10$  mm was seen in 17 patients. Postoperative histology revealed that 17 patients had benign IPMNs, which were either adenomas (n=11), or a borderline lesion (n=6). Of the 46 patients, 29 (63%) showed malignant IPMNs; these cases consisted of non-invasive carcinomas (n=13), minimally invasive carcinomas (n=8), and invasive carcinomas (n=8).

#### **Repeated pancreatectomy (Table 3)**

Among the patients who underwent pancreatic surgery, 3 patients underwent repeated pancreatectomy. Among these 3 patients, TP was performed after DP in 2 cases and after PPPD in 1 case. Histological findings at the initial procedure revealed minimally invasive carcinoma in 2 patients and invasive carcinoma in 1 patient. The intervals between initial resection and TP were 49, 48, and 19 months, respectively. The recurrent histology

indicated minimally invasive carcinomas in all 3 patients, and all 3 patients showed disease-free survival.

#### **Cause of death**

The median postoperative follow-up period was 68.4 months (range 12-189 months). Three of the 46 patients with main duct IPMN died of tumor recurrence. Among the 3 patients with tumor recurrence, 2 patients died of peritoneal dissemination and the remaining patient died of liver metastasis. All 3 patients with tumor recurrence showed invasive IPMN by the initial histology. Two of these patients died of colon cancer, and the remaining patient died of the rupture of pseudoaneurysm due to the pancreatic fistula one month after surgery (Table 4).

## **Discussion**

The incidence of malignancy in main duct IPMNs is high.<sup>7-10</sup> Therefore, the recommended management of main duct IPMNs is surgical resection according to the international consensus guideline for the management of IPMNs.<sup>2</sup> IPMNs tend to show a longitudinal wide spreading into the pancreatic duct. Okada et al.<sup>18</sup> reported that the distance of tumor spread in the main pancreatic duct was  $41.6 \pm 30.0$  mm. On the other hand, dilatation of the main duct IPMN may be related to not only a neoplasm spread widely along the main pancreatic duct, but also to the overproduction of mucus and/or associated chronic pancreatitis.<sup>13</sup> In brief, there may be a discrepancy between the lesion of the ductal dilatation and the actual localization of neoplasm of main duct IPMN. For this reason, it is often difficult to determine the appropriate resection line of the pancreas in main duct IPMNs. Ito et al.<sup>11</sup> reported that total pancreatectomy is indicated for main duct IPMNs when dilatation of the main duct suggests a neoplasm spreading throughout the whole pancreas. However, total pancreatectomy results in severe and permanent endocrine and exocrine pancreatic insufficiency. Crippa et al.<sup>10</sup> recommended

that the decision to perform total pancreatectomy should be made following consideration of the surgical risk and long-term complications. In this study, only 1 patient underwent total pancreatectomy at the initial surgical procedure. In addition, 3 patients underwent total pancreatectomy as repeated pancreatectomy for recurrent minimally invasive IPMN. Nakagohri et al.<sup>19</sup> reported that there was no significant difference in survival between noninvasive/minimally invasive IPMNs of the main duct-type and those of the branch duct-type, and noninvasive/minimally invasive IPMNs had a favorable prognosis after surgical treatment. Therefore, total pancreatectomy should be considered very selectively in the presence of a malignant lesion spreading to the whole pancreas. Among the 6 patients who died in the present study, no deaths occurred due to local recurrence. All recurrences occurred as peritoneum dissemination in this series. In their study, Takahashi et al.<sup>20</sup> suggested that peritoneal dissemination occurred for peritoneal seeding of tumor cells as a result of the leakage of pancreatic juice. We and other pancreatic surgeons should pay more attention to the meticulous manipulations needed to avoid tumor-cell seeding during these surgical procedures.

In conclusion, the routine performance of total pancreatectomy for the treatment of main duct IPMNs is not acceptable. Although total pancreatectomy has the potential to improve the long-term prognosis for patients with main duct IPMNs, it can also lead to severe and permanent endocrine and exocrine pancreatic insufficiency. We believe that it is important to perform sufficient and appropriate pancreatic resection for malignant lesions of main duct IPMN and to perform meticulous screening for the remnant pancreas following the initial pancreatic resection.

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Table 1. Characteristics of resected main pancreatic duct type intraductal papillary mucinous neoplasms

Characteristics	Data
Age (yr)	68.5 ± 9.8
Sex (M/F)	29 / 17
Symptoms (n)	
Asymptomatic	29
Abdominal pain	12
Jaudice	2
Loss of weight	2
Back pain	1
OGTT (n)	
Normal	26
Impaired, diabetic	20
HbA1c (%)	6.3 ± 1.6
BT-PABA test (%)	57.1 ± 19.2

OGTT, oral glucose tolerance test; HbA1c, hemoglobin A1c; BT-PABA, N-benzoyl-tyrosyl-p-aminobenzoic acid;

Table 2. Operative characteristics of resected main pancreatic duct type intraductal papillary mucinous neoplasms

Characteristic	Data
Operative procedure (n)	
PPPD	15
Lap-PPPD	6
DP	6
PD	5
PHRSD	5
DPPHR	3
MP	3
Lap-DP	2
TP	1
Maximum diameter of main pancreatic duct (n)	
< 10 mm	22
> 10 mm	24
Mural nodule (n)	
Not detected	20
< 10 mm	9
> 10 mm	17
Histology (n)	
Adenoma	11
Borderline	6
Non-invasive carcinoma	13
Minimally invasive	8
Invasive carcinoma	8

PPPD, pylorus-preserving pancreaticoduodenectomy; Lap-PPPD, laparoscopic pylorus-preserving pancreaticoduodenectomy; DP, distal pancreatectomy; PD, pancreaticoduodenectomy; PHRSD, pancreatic head resection with segmental duodenectomy; DPPHR, duodenum-preserving pancreatic head resection; MP, middle pancreatectomy; Lap-DP, laparoscopic distal pancreatectomy; TP, total pancreatectomy.

Table 3. Summary of three patients who underwent repeated pancreatectomy

No.	Age (yr)	Sex	Initial procedure	Initial histology	Interval from Initial Surgery (mo)	Recurrent histology	Prognosis(mo)
1	67	M	DP	minimally invasive	49	minimally invasive	DF, 15
2	80	M	DP	invasive carcinoma	48	minimally invasive	DF, 8
3	82	F	PPPD	minimally invasive	19	minimally invasive	DF, 19

DP, distal pancreatectomy; PPPD, pylorus-preserving pancreaticoduodenectomy; DF, disease free

Table 4. Summary of patient deaths of main pancreatic duct type intraductal papillary mucinous neoplasms

No.	Age (yr)	Sex	Procedure	Initial histology	Cause of death	Survival (mo)
1	66	F	PPPD	non invasive	colon cancer	136
2	55	F	PD	invasive carcinoma	recurrence (liver metastasis)	6
3	68	M	PD	invasive carcinoma	recurrence (peritoneum dissemination)	21
4	71	M	MP	borderline	rupture of pseudoaneurysm	1
5	72	M	TP	invasive carcinoma	recurrence (peritoneum dissemination)	16
6	66	M	DP	minimally invasive	colon cancer	17

PPPD, pylorus-preserving pancreaticoduodenectomy; PD, pancreaticoduodenectomy; MP, middle pancreatectomy; TP, total pancreatectomy; DP, distal pancreatectomy.