Original Article

Stenting Versus Non-stenting in Pancreaticojejunostomy:

A Prospective Study that is limited to a normal pancreas without

fibrosis sorted by using Dynamic Magnetic Resonance Imaging

Tamotsu Kuroki, MD, Yoshitsugu Tajima, MD, Amane Kitasato, MD,

Tomohiko Adachi, MD, and Takashi Kanematsu, MD

Department of Surgery, Nagasaki University Graduate School of

Biomedical Science, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan.

Running Title: Stenting versus Non-stenting in

pacreaticojejunostomy.

Please address reprint requests to: T. Kuroki

Fax: +81-95819-7319

E-mail: tkuroki-gi@umin.ac.jp

Abstract

Objectives: Pancreatic duct stenting has been reported to reduce pancreatic fistula after pancreaticojejunostomy, but the previous studies were not conducted under a standardized assessment of the nature of the pancreas such as the degree of pancreatic fibrosis. We prospectively investigated the efficacy of an external pancreatic duct stent to prevent pancreatic fistula in the non-fibrotic pancreas after pancreaticojejunostomy, in which the degree of pancreatic fibrosis was assessed objectively by using dynamic magnetic resonance imaging (MRI).

Methods: Among the 67 consecutive patients who underwent pancreatic head resection, 45 patients were judged to have a normal pancreas without fibrosis based on the preoperative assessment of pancreatic fibrosis based on dynamic contrast-enhanced MRI. The patients were randomly allocated to one of two groups with (n=23) or without (n=22) use of an external pancreatic duct stent in performing a pancreaticojejunostomy.

Results: Pancreatic fistula developed in 8 (34.5%) patients the stented group, 3 grade A and 5 grade B; while in the non-stented group 9 (40.9%) patients developed pancreatic fistula, 3 grade

A and 6 grade B. There were no significant differences in the incidence or severity of pancreatic fistula between the two groups.

Conclusions: The utility of the external pancreatic duct stent after pancreaticojejunostomy was not found in the non-fibrotic pancreases which were sorted according to the degree of pancreatic fibrosis using the pancreatic TIC analysis from dynamic contrast-enhanced MRI.

Key words: Stenting, non-stenting, dynamic magnetic resonance imaging, time-intensity curve, pancreatic fibrosis, pancreatic fistula, pancreaticojejunostomy.

Introduction

Recent advances in surgical techniques and a better understanding of surgical pancreatic anatomy have made it possible to safely perform a variety of techniques for pancreatic resection, including classic pancreaticoduodenectomy (PD), pylorus-preserving pancreaticoduodenectomy (PPPD), duodenum-preserving pancreatic head resection (DPPHR), and segmental pancreatic resection (SPR), in the treatment of benign and malignant pancreatic and periampullary diseases. The hospital mortality rate after pancreatic surgery has decreased in recent years, but the morbidity rate remains high.[1-3] Pancreatic fistula is one of the most common and serious complications after pancreaticoenteric anastomosis in pancreatic surgery, and various surgical techniques and devices have been proposed to prevent fistula formation.[4-6] The placement of a transanastomotic stent for internal or external drainage of pancreatic secretion has been advocated to prevent pancreatic fistula,[7-9] and conversely, the usefulness of non-stented pancreaticoenteric anastomosis has been reported by some groups.[10, 11] Another group has reported observing no benefit for the pancreatic duct stenting following

4

PD in a prospective randomized trial.[12]

Several risk factors for postoperative pancreatic fistula have been reported, including the texture of the remnant pancreatic parenchyma.[13-15] It is well known that the degree of pancreatic fibrosis greatly influences the texture of the pancreatic gland. Recently, we have demonstrated that the time-signal intensity curve (TIC) of the pancreas obtained from dynamic contrast-enhanced magnetic resonance imaging (MRI) is a reliable indicator of pancreatic fibrosis, by reflecting the histological degree of pancreatic fibrosis.[16] The patterns of pancreatic TIC were classified into three types according to the time to peak after the bolus injection of contrast material: namely, types I, II, and III. The type I pancreatic TIC indicated a normal pancreas without fibrosis, and types II and III indicated a fibrotic pancreas. In addition, our recent report found that type I pancreatic TIC is a significant risk factor for pancreatic fistula formation after pancreaticojejunostomy, and the pancreatic TIC profile reflected the anatomic condition of the pancreatic remnant related to pancreatic fistula formation more precisely than intra-operative assessment of the pancreas by the

surgeon's hands.[17] Thus, we designed a prospective randomized trial to investigate whether pancreatic duct stenting in pancreaticojejunostomy affects pancreatic fistula formation following pancreatic head resection in patients with a soft pancreas without fibrosis demonstrating the type I pancreatic TIC.

Patients and Methods

The study protocol was approved by the Institutional Review Board of Nagasaki University Hospital (IRB 07050267), and informed consent was obtained from all patients participating in the trial before surgery. Between May 2006 and October 2009, 67 consecutive patients underwent pancreatic resection followed by an end-to-side, duct-to-mucosa pancreaticojejunostomy for pancreatic and periampullary diseases. They included 33 men and 34 women with a mean age of 69 years (range 38 to 86 years).

All 67 patients underwent dynamic contrast-enhanced MRI of the pancreas prior to surgery. The procedures for pancreatic TIC analysis have been described in detail elsewhere.[16] Briefly, the dynamic series comprised five individual dynamic images, obtained before as well as 25 seconds and 1, 2, and 3 minutes after the rapid bolus injection of meglumine gadopentetate (Magnevist®; Schering, Berlin, Germany). The patterns of pancreatic TIC were classified into three types according to the time to peak: 25 s, 1 min, or 2 min after the bolus injection of contrast material; namely, types I, II, and III, respectively (Fig. 1). In strict accordance with the pancreatic TIC profile, the patients were

7

divided into two groups: patients with type I pancreatic TIC, thus indicating a normal pancreas without fibrosis, and patients with type II or III pancreatic TIC, signifying fibrotic pancreas.[16,17] The patients with type I pancreatic TIC, before understanding pancreaticojejunostomy, were allocated to one of two groups by an equal number of blind envelopes: a stented group and a non-stented group. In contrast, the patients with type II or III pancreatic TIC were excluded from the study because the previous study demonstrated that pancreatic fistula rarely develops after pancreaticojejunostomy in patients with type II or III pancreatic TIC.[17]

Surgical Technique

The surgical technique of pancreaticojejunostomy was standardized except for placement of the external pancreatic duct stent in the stented group. An end-to-side, duct-to-mucosa anastomosis between the pancreas and jejunum was created in two layers of sutures. The inner layer was composed of the pancreatic duct and the entire jejunal wall using interrupted 5-0 absorbable sutures. The outer layer was composed of the pancreatic parenchyma and the seromuscular layer of the jejunum using interrupted 4-0

nonabsorbable sutures. In the stented group, a 5-French diameter
pancreatic drainage tube with multiple side-holes was used for
the pancreatic duct and brought out via an enterotomy in the free
end of the jejunal loop. The enterotomy site was closed tightly
with a purse-string suture to prevent pancreatic drainage tube
migration. No sealants were used in either group. Two closed
suction drains were routinely placed near the biliary and
pancreatic anastomoses.

Pre-, intra-, and post-operative data

The preoperative data obtained included age, gender, the
diagnosis of pancreatic and periampullary diseases, preoperative
body mass index (BMI), the concentrations of serum albumin, total
bilirubin, results of the oral glucose tolerance test (OGTT),
hemoglobin A1c (HbA1c) levels, *N*-benzoyl-tyrosyl-*p*-aminobenzoic
acid (BT-PABA) test results, and the pancreatic TIC profile
examined at the proposed transection line for the pancreas. An
abnormal glycemic response to the OGTT was defined according to
the criteria proposed by the World Health Organization study group
on diabetes mellitus.[18]

Intraoperative data obtained included the type of

pancreatic resection (PPPD, PD, SPR, DPPHR, or pancreatic head resection with segmental duodenectomy (PHRSD)), lymphadenectomy (non or regional), diameter of the main pancreatic duct ($\leqq$3mm or > 3mm), operative time, intraoperative bleeding, and red blood cell transfusion. The diameter of the main pancreatic duct was measured at the cut surface of the pancreatic remnant.

Data on the postoperative course and complications were collected. Amylase levels of the drainage fluid were measured on postoperative days (PODs) 1, 3, and 5, respectively.

Study End Point

The primary study end point was pancreatic fistula. Pancreatic fistula was defined as the output via a peripancreatic drain of any measurable volume of drainage fluid, on or after POD3, associated with an elevated amylase content greater than three times the upper limit of the normal serum amylase value (>390 IU/L), according to the International Study Group on Pancreatic Fistula (ISGPF) definition.[19] The severity of postoperative pancreatic fistula was classified into three grades as follows: grade A, transient, asymptomatic fistulas with elevated amylase levels only in the drainage fluid, for which treatments or deviation in

clinical management are not required; grade B, clinically apparent, symptomatic fistulas requiring diagnostic evaluation and therapeutic management; and grade C, severe fistulas requiring major deviations in clinical management and aggressive therapeutic intervention.[19]

Statistical analyses

Continuous data are expressed as mean $\pm$ SD. The eight preoperative and six intraoperative parameters were registered as presumed risk factors for postoperative pancreatic fistula. Statistical analysis was carried out using either the Mann-Whitney *U* test or Fisher's exact test. Differences were considered significant at *P* < 0.05.

Results

The pancreatic TIC profiles were type I in 45 patients, type II in 21, and type III in 1. Therefore, 45 patients with type I pancreatic TIC were enrolled in the prospective randomized study. Of these, 23 were randomized to the stented group and 22 to the non-stented group (Fig. 2). These 45 patients underwent a pancreaticojejunostomy by two different senior surgeons.

The preoperative data of the two study groups are compared in Table 1. There were no significant differences in patient age, gender, diagnosis, BMI, and preoperative laboratory parameters between the groups. The groups were also similar in the glycemic response to OGTT, HbA1c levels, and BT-PABA test results.

The intraoperative data for the two study groups are shown in Table 2. The two study groups were comparable with regard to the type of pancreatic resection, lymphadenectomy, main pancreatic duct size, operative time, intraoperative blood loss, and blood transfusion requirements.

Postoperative pancreatic fistula was identified in 8 (34.5%) patients in the stented group, and was classified as grade A, being transient and asymptomatic with only elevated drain

amylase values in 3 patients, and as grade B in 5 patients, who required percutaneous drainage of an amylase-rich or infected peripancreatic intra-abdominal collection (Table 3). Whereas in the non-stented group, pancreatic fistula occurred in 9 (40.9%) patients, as grade A in 3 and grade B in 6. There was no case of grade C pancreatic fistula in this study. As a result, there were no significant differences in the occurrence and severity of postoperative pancreatic fistula between the two study groups.

Discussion

Pancreatic fistula, which is often associated with subsequent abdominal abscess, sepsis, and erosive hemorrhage, is the most problematic complication and represents a leading cause of morbidity and mortality after pancreatic head resection.[1-6] Several studies have shown that non-fibrotic soft pancreas is one of the most important risk factors for postoperative pancreatic fistula formation after pancreaticoduodenectomy.[13-15] Therefore, pancreatic duct stenting is generally utilized for performing pancreaticojejunostomy especially in patients with a non-fibrotic soft pancreas. Poon et al.[20] have suggested that a pancreatic duct stent following pancreaticojejunostomy may help divert pancreatic secretions away from the anastomosis, thus allowing more precise sutures for the prevention of suture injury and the iatrogenic pancreatic duct occlusion. On the other hand, several complications associated with the placement of pancreatic duct stents such as accidental pulling out of the stent and chronic/acute pancreatitis due to obstruction of the stent tube have been reported, and these drawbacks may create a predisposition to pancreatic fistula formation.[10,11,21] Winter et

al.[12] have conducted a prospective randomized trial in which subjects either received an internal pancreatic duct stent or no stent during pancreaticojejunostomy, with two arms stratified according to the texture of the remnant pancreas (soft/normal versus hard). They concluded that the pancreatic stent does not decrease the frequency or severity of pancreatic fistula, even in soft pancreas. However, judgments regarding the texture of the pancreatic remnant has been made based on the surgeon's palpation at the time of surgery, with the remnant being classified as soft, fragile, intermediate, sclerotic, or hard, in previous studies related to pancreatic fistula after pancreaticoenterostomy. In other words, the pancreatic texture has been estimated just as a "subjective" parameter. It is therefore necessary to standardize the measure in evaluating the anatomic condition of the pancreatic remnant when we investigate the efficacy of the pancreatic duct stent during pancreaticojejunostomy. In the present study, the patients undergoing a pancreatic head resection were sorted in strict accordance with the pancreatic TIC profile from dynamic contrast-enhanced MRI because the pancreatic TIC analysis can estimate the histological degree of pancreatic fibrosis prior to

surgery and also better indicates the anatomic condition of the
pancreatic remnant related to pancreatic fistula formation than
the surgeon's hands.[16,17] The fibrosis ratios of pancreases with
type I, II, or III TICs are 3.5%, 15.9%, and 22.6%, respectively,[16]
with pancreatic fistula developing in only 1 of 37 patients (3%)
with type II or III pancreatic TIC, whereas 13 of the 52 patients
(25%) with type I pancreatic TIC display pancreatic fistula after
a pancreaticojejunostomy.[17] The present study, utilizing
pancreatic TIC analysis as an "objective" parameter for evaluating
the nature of the remnant pancreas, clearly demonstrated that no
observable benefit for the pancreatic duct stent in preventing
pancreatic fistula after pancreaticojejunostomy in the
non-fibrotic pancreas. Winter et al.[12] have reported a prospective
randomized study of 113 patients with a soft pancreas showing that
internal pancreatic duct stents do not decrease the pancreatic
fistula rate from 33.9% in the no-stent group to 47.4% in the stent
group. Our prospective randomized study demonstrated a similar
result with a pancreatic fistula rate of 40.9% in the no-stent
group and 34.5% in the stent group. Furthermore, our study showed
that external pancreatic duct stent had no effect on preventing

aggravation of the pancreatic fistula after

pancreaticojejunostomy, i.e., grade B pancreatic fistula was

recognized in 5 patients in the stented group and in 6 patients

in the non-stented group.

Pancreaticojejunostomy in the present study was achieved

by a double-layer method, consisting of a duct-to-mucosa

anastomosis for the inner layer and an approximation between the

pancreatic stump and the jejunum for the outer layer. In a canine

model, Greene et al.[22] have reported that duct-to-mucosa

anastomosis is superior to invagination anastomosis in terms of

anastomotic patency and remnant pancreatic function. Several

retrospective reports have demonstrated that duct-to-mucosa

anastomosis may be associated with a lower pancreatic fistula rate

than invagination anastomosis.[23-25] However, Marcus et al.[26] have

reported that duct-to-mucosa anastomosis has a significantly

lower pancreatic fistula rate than invagination anastomosis in

low-risk patients, whereas invagination anastomosis is a safer

technique than duct-to-mucosa anastomosis in high-risk patients

with small pancreatic ducts or a soft pancreas. Ultimately, a

prospective randomized trial in a various combination depending

on the risk of pancreatic fistula and surgical technique will be required to determine the best superior anastomosis for the prevention of pancreatic fistula after pancreaticojejunostomy.

In conclusion, the utility of the external pancreatic duct stent after pancreaticojejunostomy was not found in the non-fibrotic pancreases, which were standardized based on the objective assessment of pancreatic fibrosis using pancreatic TIC analysis from dynamic contrast-enhanced MRI.

References

1. Balcom JH, Rattner DW, Warshaw AL, et al. Ten-year experience with 733 pancreatic resections: changing indications, older patients, and decreasing length of hospitalization. Arch Surg 2001; 136: 391-8.

2. Adam U, Makowiec F, Riediger H, et al. Riskfactors for complications after pancreatic head resection. Am J Surg 2004; 187: 201-8.

3. de Castro SM, Busch OR, van Gulik TM, et al. Incidence and management of pancreatic leakage after pancreatoduodenectomy. Br J Surg 2005; 92: 1117-23.

4. Jacob DA, Bahra M, Langrehr JM. Jejunal loop drainage versus direct pancreatic duct drainage after pancreatic head resection. Surg Today 2006; 36: 898-907.

5. Hasegawa K, Kokudo N, Sano K, et al. Two-stage pancreatojejunostomy in pancreaticoduodenectomy: a retrospective analysis of short-term results. Am J Surg 2008; 196: 3-10.

6. Sugiyama M, Suzuki Y, Abe N, et al. Pancreatic duct holder for facilitating duct-to-mucosa pancreatojejunostomy after

pancreatoduodenectomy. Am J Surg 2009; 197: 18-20.

7. Poon RT, Fan ST, Lo CM, et al. External drainage of pancreatic duct with a stent to reduce leakage rate of pancreaticojejunostomy after pancreaticoduodenectomy: a prospective randomized trial. Ann Surg 2007; 246: 425-35.

8. Kamoda Y, Fujino Y, Matsumoto I, et al. Usefulness of performing a pancreaticojejunostomy with an internal stent after a pancreatoduodenectomy. Surg Today 2008; 38: 524-8.

9. Kimura W. Pancreaticojejunal anastomosis, using a stent tube, in pancreaticoduodenectomy. J Hepatobiliary Pancreat Surg 2009; 16: 305-9.

10. Imaizumi T, Harada N, Hatori T, et al. stenting is unnecessary in duct-to-mucosa pancreaticojejunostomy even in the normal pancreas. Pancreatology 2002; 2: 116-21.

11. Imaizumi T, Hatori T, Tobita K, et al. Pancreaticojejunostomy using duct-to-mucosa anastomosis without a stenting tube. J Hepatobiliary Pancreat Surg 2006; 13: 194-201.

12. Winter JM, Cameron JL, Campbell KA, et al. Does pancreatic duct stenting decrease the rate of pancreatic fistula following pancreaticoduodenectomy? Results of a prospective randomized

trial. J Gastrointest Surg 2006; 10: 1280-90.

13. Yeo CJ, Cameron JL, Lillemoe KD, et al. Does prophylactic octreotide decrease the rates of pancreatic fistula and other complications after pancreaticoduodenectomy? Results of a prospective randomized placebo-controlled trial. Ann Surg 2000; 232: 419-29.

14. Sato N, Yamaguchi K, Chijiiwa K, Tanaka M. Risk analysis of pancreatic fistula after pancreatic head resection. Arch Surg 1998; 133: 1094-8.

15. Cheng Q, Zhang B, Zhang Y, et al. Predictive factors for complications after pancreaticoduodenectomy. J Surg Res 2007; 139: 22-9.

16. Tajima Y, Matsuzaki S, Furui J, et al. Dynamic magnetic resonance imaging to evaluate remnant pancreatic fibrosis. Br J Surg 2004; 91: 595-600.

17. Tajima Y, Kuroki T, Tsutsumi R, et al. Risk factors for pancreatic anastomotic leakage: the significance of preoperative dynamic magnetic resonance imaging of the pancreas as a predictor of leakage. J Am Coll Surg 2006; 202: 723-31.

18. World Health Organization. Report of the expert committee on

the diagnosis and classification on diabetes mellitus. Diabetes Care 1997; 20: 1183-97.

19. Bassi C, Dervenis C, Butturini G, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 2005; 138: 8-13.

20. Poon RT, Lo SH, Fong D, et al. Prevention of pancreatic anastomotic leakage after pancreaticoduodenectomy. Am J Surg 2002; 183: 42-52.

21. Ammori BJ, White CM. Proximal migration of transanastomotic pancreatic stent following pancreaticoduodenectomy and pancreaticojejunostomy. Int J Pancreatol 1999; 25: 211-5.

22. Greene BS, Loubeau JM, Peoples JB, Elliott DW. Are pancreatoenteric anastomoses improved by duct-to-mucosa sutures? Am J Surg 1991; 161: 45-50.

23. Bartoli FG, Arnone GB, Ravera G, et al. Pancreatic fistula and relative mortality in malignant disease after pancreaticoduodenectomy. Review and statistical meta-analysis regarding 15 years of literature. Anticancer Res 1991; 11: 1831-48.

24. Matsumoto Y, Fujii H, Miura K, et al. Successful

pancreatojejunal anastomosis for pancreatoduodenectomy. Surg Gynecol Obstet 1992; 175: 555-62.

25. Howard JM. Pancreatojejunostomy: leakage is a preventable complication of the Whipple resection. J Am Coll Surg 1997; 184: 454-7.

26. Marcus SG, Cohen H, Ranson JH. Optimal management of the pancreatic remnant after pancreaticoduodenectomy. Ann Surg 1995; 221: 635-48.
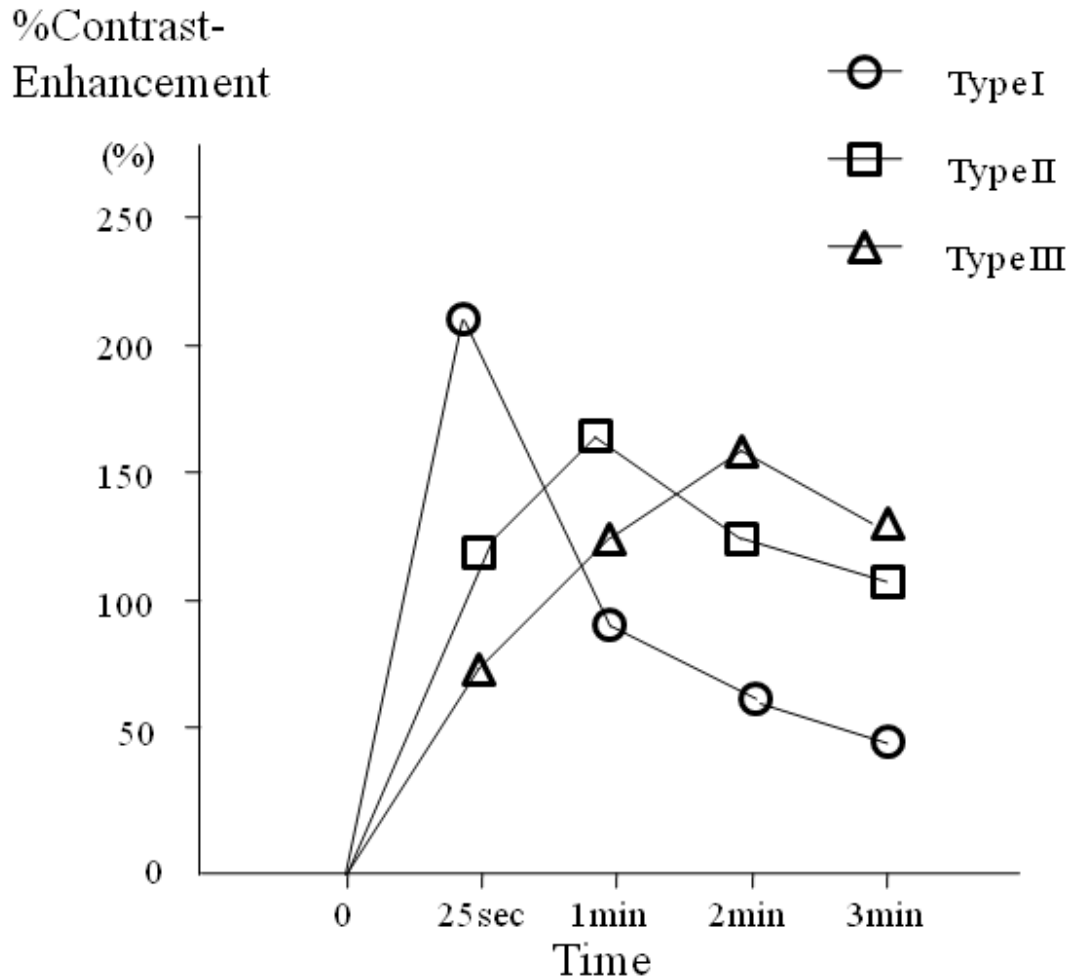
Figure legends

Figure 1. Patterns of the time-signal intensity curve (TIC) from dynamic MRI of the pancreas. Type I TIC exhibits a rapid rise to a peak (25 sec after injection) followed by a rapid decline. Type II and III TICs have a slow rise to a peak (1 or 2 min after injection) followed by a slow decline or plateau, respectively.
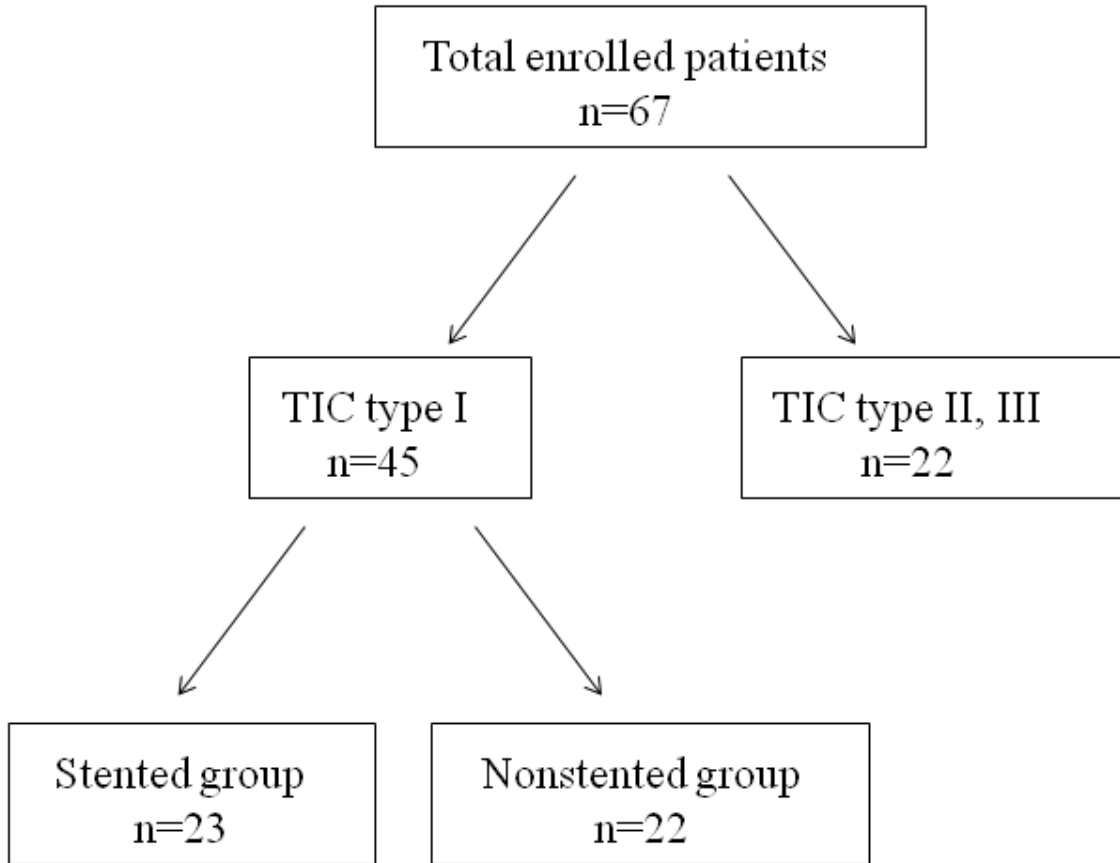
24

Figure 2. The distribution of patients in each enrolled group.

Forty-five patients showed type I pancreatic TIC and 22 patients

showed type II or III pancreatic TIC. Of the patients with TIC

type I, 23 were randomized to the stented group and 22 to the

non-stented group.

Table 1. Demographic data of the patients

| | TIC type I (n=45) | | *P* value |
	Stented group (n=23)	Nonstented group (n=22)	
Age, y	68.1±11.2	68.2±8.4	NS
Male/Female, n	13/10	12/10	NS
Diagnosis, n			NS
IPMN of the pancreas	5	8	
Pancreatic cancer	3	5	
Bile duct carcinoma	10	6	
Ampullary carcinoma	4	1	
Others	1	2	
Preoperative BMI, kg/m2	21.0±2.8	21.9±3.0	NS
Preoperative serum bilirubin, mmol/L	1.9±1.9	1.5±2.0	NS
Preoperative serum albumin, g/dL	3.7±0.5	3.9±0.5	NS
Lymphocyte, 1000/mm3	1.5±0.7	1.5±0.6	NS
OGTT, n			NS
Normal	18	15	
Impaired, diabetic	5	7	
HbA1c, %, n			NS
$\leqq 6.0$	18	14	
> 6.0	5	8	
BT-PABA test, %	65.3±13.4	62.4±16.5	NS

IPMN , intraductal papillary mucinous neoplasm; BMI, body mass index; OGTT, oral glucose tolerance test;

HbA1c, hemoglobin A1c; BT-PABA, *N*-benzoyl-tyrosyl-*p*-aminobenzoic acid; TIC, time-signal intensity curve;

NS, not significant.

Table 2. Intraoperative data

	TIC type I (n=45)		*P* value
	Stented group (n=23)	Nonstented group (n=22)	
Type of　pancreatic resection, n			NS
PPPD	16	11	
PD	2	3	
Segmental Pancreatectomy	3	1	
PHRSD	1	6	
DPPHR	1	1	
Lymphadenectomy, n			NS
Non	5	8	
Regional	18	14	
Main pancreatic duct size, mm			NS
≦3.0	19	16	
> 3.0	4	6	
Operative time, min	591.0±174.0	647.8±240.9	NS
Intraoperative bleeding, ml	1243.6±902.5	1363.6±1084.1	NS
Red blood cell transfusion, n			NS
With	7	9	
Without	16	13	

PPPD , pancreaticoduodenectomy; PPPD, pylorus-preserving pancreaticoduodenectomy;

PHRSD, pancreatic head resectionwith segmental duodenectomy; DPPHR,deodenum-preserving pancreatic head resection;

NS, not significant.

Table 3. Postoperative pancreatic fistula rates in TIC type I

	TIC type I (n=45)		
	Stented group (n=23)	Nonstented group (n=22)	*P* value
Pancreatic fistula, ISGPF, n			NS
Grade A	3	3	
Grade B	5	6	
Grade C	0	0	

ISGPF ,International Study Group onPancreatic Fistula.