Table 1 Primers used in the present study. The hepatocyte specific gene expression levels were determined by using RT-PCR method. As hepatocyte specific parameters, albumin and CYP3A2 were selected. As an internal control, GAPDH gene expression was also examined. The primer sequences and optimal PCR conditions were summarized.

Gene	Sequence (5'-3' sense/antisense)	Reaction condition			Product size	Cycles
		Denaturation	Annealing	Elongation		
GAPDH	TTCAACGGCACAGTCAAG CACACCCATCACAAACAT	95℃, 1 min	60℃, 1 min	72℃, 2 min	240 bp	26
CYP3A2	TACTACAAGGGCTTAGGGAG CTTGCCTGTCTCCGCCTCTT	94℃, 1 min	60℃, 1 min	72℃, 2 min	348 bp	27
ALB	ATACACCCAGAAAGCACCTC CAGAGTGGAAGGTGAAGGTC	94℃, 1 min	60℃, 1 min	72℃, 2 min	305 bp	27

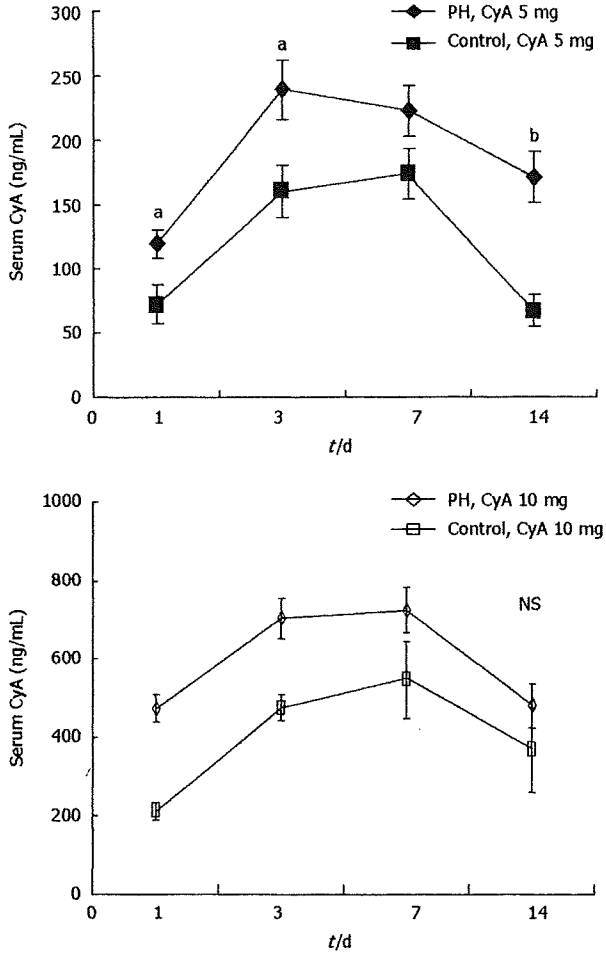

Figure 2 Changes in the serum concentration of CyA during liver regeneration. The values are expressed as the mean ± SD of 5 samples in each group. The concentration of CyA reached a maximum during 3 to 7 d, and gradually declined thereafter. The level of CyA in the PH group was significantly higher than that in control group. $^{a}P < 0.05$, $^{b}P < 0.01$.

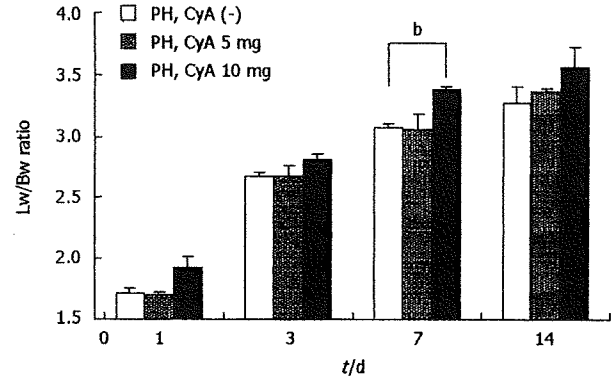

Figure 3 The effect of CyA on the liver regeneration ratio. The values are expressed as the mean ± SE of 5 samples in each group. The low concentration of CyA (5 mg) did not affect the liver regeneration potential during the observation period; however, the rate of liver regeneration was significantly higher than that in the-low CyA group on postoperative day 7. $^{b}P < 0.01$.

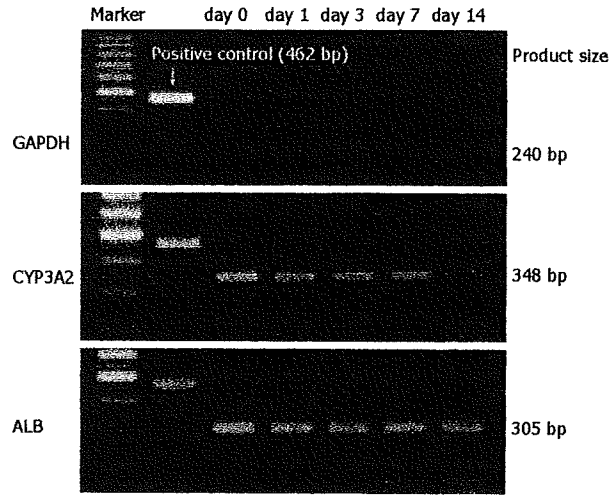

Figure 4 Changes of hepatocyte specific gene expression during liver regeneration. Alb mRNA expression remained constant during liver regeneration, while the hepatocyte specific p450 activity-CYP3A2 significantly decreased on postoperative day 14.

DISCUSSION

The present study, investigated the pharmacokinetics of the CyA in a rat two thirds hepatectomy model, for the first time. The results yielded important information concerning the interrelationship between the CyA and regenerating liver. (1) The metabolism is retarded in a regenerating liver, which is actually seen in clinical partial liver transplantation. (2) CyA has possible hepatotrophic effect on the regenerating liver in a CyA-dose dependent manner. (3) The p450 activity of the regenerating liver was down-regulated after CyA administration.

As expected, the serum concentrations of CyA after

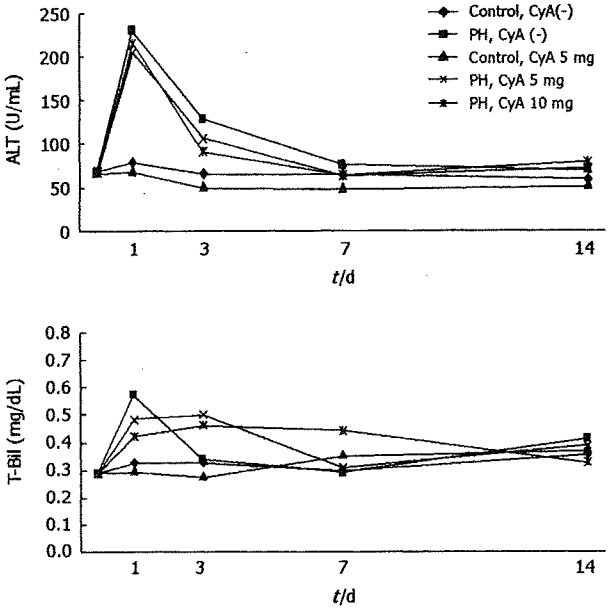

Figure 5 The effect of CyA on liver function. Rats were anesthetized and blood samples were collected through the tail vein at the indicated time points. ALT and T-Bil level were measured as indicators of liver function. On day 1, ALT level were significantly increased and thereafter gradually reduced. There was no statistically significant difference in each group ($P > 0.05$).

a hepatectomy were significantly higher than that seen in the sham operated group as previously reported in clinical settings. There are several possible explanations for this, including increased absorption, decreased volume of distribution, or decreased clearance.

However, an increased absorption is not likely. The CyA used in this study was the microemulsified type, and the absorption is bile independent. Therefore, absorption of the CyA was table in both groups[9]. The volume of distribution should be smaller in the partially hepatectomized rats. In other words, a smaller volume of distribution could increase the relative blood level of an immunosuppressant for a given dose.

Another possibility for the higher levels of CyA after the partial hepatectomy is reduced hepatic immunosuppressive clearance, which may be explained by two possible mechanisms. One is simply because of the reduced hepatic mass available to metabolize the drugs. Another possibility is that immediately after hepatectomy, the hepatic mass is reduced because of the surgical excision of hepatic tissue. As a result, the ability to clear substances through the liver is reduced. For instance, the indocyanine green half-life is increased four-fold after a 60% hepatectomy and by 33% after a 40% hepatectomy[10]. In the rats after a two thirds hepatectomy, the whole-organ reduced form of-cytochrome c reductase and cytochrome p-450 activity are reduced by half. After a 90% hepatectomy, galactose clearance in rats was reduced by 90% within 24 h after surgery. The genetic data regarding the cytochrome p-450 gene suggested that the metabolic activity of specific enzymes responsible for drug metabolism is reduced in the remaining hepatic tissue. Marie *et al* reported that the cytochrome p-450 activity decreased soon after a two-thirds hepatectomy in rats, returning to 90% of the initial activity 2 wk postoperatively. In the present study, the expression analysis of cytochrome p450 activity was performed using RT-PCR method. The results showed the cytochrome p-450 activity remained at the initial stage of liver regeneration, finally declined in the late stages. Although, no other liver specific enzymes were examined, a previous study demonstrated that the levels of mRNA for enzymes responsible for gluconeogenesis and the acute phase proteins are increased up to four fold after a hepatectomy[11]. Therefore, there are adaptive changes in the hepatic tissue after a partial hepatectomy. Collectively, the activity of enzymes that support hepatic regeneration is increased, whereas the activity of the enzymes responsible for drug metabolism is reduced.

The present data also suggest that cyclosporine enhances the hepatic regenerative response without affecting the individual hepatocellular function. Among immunosuppressive drugs currently in clinical use, azathioprine and steroids have been reported to exert an antiproliferative action on the regenerating liver. Azathioprine inhibits the DNA or RNA synthesis of hepatocytes, acting as an antimetabolite, whereas the action of steroids is more complex. Several investigators have suggested a functional linkage between lymphoid tissues and hepatocytes. Craddock *et al* reported that a partial hepatectomy induced proliferation of hepatocytes as well as lymphoid tissues. Another study recently suggested a very close and positive interrelationship between hepatocyte replication and lymphocyte activities[12]. The new potent immunosuppressor, cyclosporin A has been extensively compared with azathioprine and steroids. It primarily inhibits T-lymphocyte responses, and has no functional effects on other hematopoietic cells or phagocytic cells[13-16]. The present study on hepatectomized rats confirmed the antimitotic action of these immunosuppressants on hepatocytes, although the degree of suppression was less than that seen in previous reports.

Notably, there seems to be some discrepancy in these data showing that the statistical difference of the serum concentration of CyA between 5 mg treated and control animals was not observed in the groups treated with 10 mg of CyA treated as demonstrated in Figure 2. However, this is probably a reflection of-the fact that the liver regenerative effect of CyA at a higher dose may improve the impaired metabolic potential for CyA itself.

The limitation of this study is that this model potentially does not require immunosuppresion; therefore, further research will be needed to elucidate the underlining mechanism for these findings in a partial liver transplant model.

In conclusion, these results indicate that CyA levels in hepatectomized rats were significantly higher in control rats without a hepatectomy, probably because of the decreased volume of distribution, and/or decreased clearance by reduced metabolic activity. The possible hepatotrophic effect of CyA on the regenerating liver has also been confirmed.

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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Actual therapeutic efficacy of pre-transplant treatment on hepatocellular carcinoma and its impact on survival after salvage living donor liver transplantation

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Abstract
Background The exact efficacy of pre-liver transplant (LT) therapy for hepatocellular carcinoma (HCC) and the impact on survival after LT remain controversial in regard to salvage LT.
Materials and methods Of 79 patients transplanted in Nagasaki University Hospital between August 1997 and December 2007, 29 patients (36.7%) were indicated for HCC based on the Milan criteria using computed tomography and magnetic resonance imaging. Pre-LT therapy other than liver resection had been performed in 18 cases (62.1%) for 24 lesions. Treated lesions were analyzed histologically using thin slices of the whole explanted liver.
Results Pre-LT therapy included transarterial chemoembolization (TACE) for 10 lesions, percutaneous ethanol injection (PEI) + TACE for 1 lesion, PEI in 6 lesions and ablation therapy in 7 lesions. Under preoperative imaging study, 19 lesions (79.1%) were "thought-to-be" necrotic by pre-LT therapy. However, histologically, viable HCCs were still observed in 9 lesions (9/19 47%). A median interval between the first pre-therapy and LT was 22 months, while last pre-LT therapy and LT was 11 months. No sarcomatous HCC or forced portal venous tumor thrombus was found in all cases with residual lesions. One peritoneal recurrence has occurred after LT, in whom PEI and RFA had been performed before LDLT. The disease free survival after LDLT was comparable to that of cases without pre-LT therapy.
Conclusion Half of the preoperatively "thought-to-be" necrotic lesions still contained viable HCC cells after the pre-LT treatment. Overall, the history of pre-LT therapy does not preclude or interfere with subsequent LT, although percutaneous treatment may spread disseminated tumor cell growth under immunosuppression.

Keywords HCC · pre-LT · Recurrence

Introduction

In Japan, where the availability of deceased liver donors is limited, hepatocellular carcinoma (HCC) is primarily treated with hepatic resection, locoregional therapy and transarterial chemoembolization [1–3]. However, when HCC recurs and further treatment is no longer possible, liver transplantation (LT) may be considered as salvage LT [4].

There are drawbacks of pre-LT treatment for HCC during the waiting period. Dissemination [5] and implantation [6] may occur after puncture of HCC and they may form tumors after the administration of immunosuppressive drugs. In addition, after incomplete locoregional therapy, sarcomatous changes have been reported [7]. With subsequent liver transplantation, damage to vital vascular structures can occur (hepatic artery, portal vein) which may affect the outcome of liver transplantation. Therefore, pre-LT therapy for HCC may increase the possibility of unfavorable changes in HCC and mask the possibility of occult HCC in a background liver, thereby compromising the

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outcome of LT. Therefore, the effect of pre-LT therapy on HCC and the outcome of LT for HCC, especially within the Milan criteria, have been reported with mixed results [8–15].

A recent paper has reported the multiple occurrence and spread of HCC in a cirrhotic liver using whole liver histological examination (WLHE). However, the exact therapeutic effect of pre-LT treatment on primary HCC has not been analyzed. Explant analyses using WLHE were used, since it is the only opportunity to investigate the true viability of HCC in thought-to-be completely necrotic lesions following pre-LT therapy in imaging. This study investigates the accuracy of pre-LT therapy for HCC and its impact on the outcome of LT.

Materials and methods

Patients

Of 79 cases transplanted in Nagasaki University Hospital before Dec. 2007, 29 cases (36.7%) were indicated for HCC within the Milan criteria and for 18 cases (62.1%), pre-LT therapy other than liver resection was performed (Fig. 1). WLHE was performed by dedicated pathologists, with 5–7 mm slices for whole liver explants. Residual HCCs after pre-LT therapy were investigated histologically in combination with various factors.

This study was approved by the local Institutional Review Board and written informed consent was obtained from all patients.

Patient characteristics

All patients were indicated for LDLT as "salvage LT". The etiology in these cases was hepatitis C virus (HCV) infection in 12 patients and hepatitis B virus (HBV) in 6 patients. There were 7 females and 11 males, with a median age of 57 years (range, 48–61 years). The median values of alpha-fetoprotein (AFP) and protein-induced vitamin K antagonists II (PIVKA-II) were 30.25 ng/ml (range 0.8–806.1) and 23 g/ml (range, 6–247).

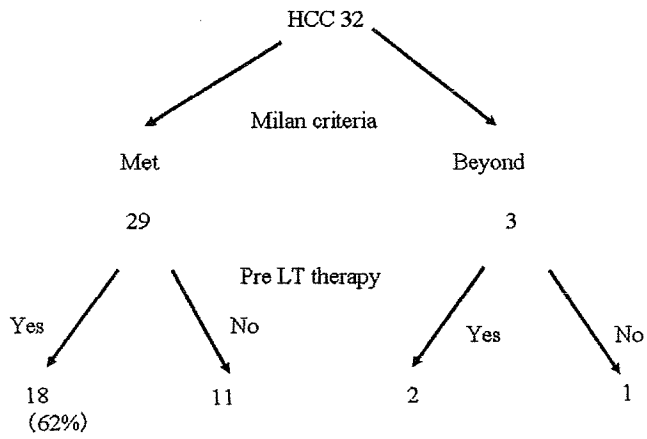

Fig. 1 Patient demographics. *LT* liver transplantation, *HCC* hepatocellular carcinoma

Liver transplantation and preoperative therapy for HCC

The median follow-up period was 24 months (range, 12–45 months). Pretreatment for HCC was performed prior to LT for 24 lesions in 18 patients, which included transarterial chemolipiodolization (TACE) in 10 lesions, radiofrequency ablation (RFA) in 7 lesions, percutaneous ethanol injection therapy (PEIT) in 6 lesions, TACE with PEIT in 1 lesion. Based on the imaging findings, all HCCs were considered to be within the Milan criteria. The clinical characteristics of the 18 patients are summarized in Table 1.

All lesions were surveyed by multidetector computed tomography scanning (MDCT) and magnetic resonance imaging (MRI) done within 1 month before transplant. Preoperatively "thought-to-be" necrotic lesions were not counted as HCC lesions under the Milan criteria. Only "thought-to-be" viable lesions evaluated by MD-CT with contrast media and MRI-SPIO were counted, which is also in accord with the Japanese national health insurance system. Preoperative imaging findings showed 5 patients with solitary viable HCC, 5 patients with double viable HCCs, 1 patient with triple viable HCCs and 7 patients with no viable HCCs. All patients met the Milan criteria with a solitary nodule 5 cm in size or 3 nodules 3 cm in size for multi-nodular HCC [18].

Whole liver histological examination (WLHE) [16]

After explantation, the cirrhotic livers were fixed in formalin for 48 h. The livers were then sectioned at

Table 1 Details in 18 patients receiving pre-LT therapy

TACE	10
Ethanol injection	6
Ablation	7
TACE + ethanol injection	1
Size of treated HCC	18 mm (10–30)
Number of therapy	2 (1–4)
Period between 1st therapy and LDLT	22 months (3–58)
Period between last therapy and LDLT	11 months (3–58)

TACE transarterial chemoembolization, *RFA* radiofrequency ablation, *HCC* hepatocellular carcinoma, *LDLT* living donor liver transplantation

5–7 mm intervals and each section was carefully inspected and mapped. All sections were embedded in paraffin and all slides were made from the paraffin-embedded material and routinely stained with hema-to_xylin and eosin. The median total number of slides for each patient was 116.5 (range, 64–185 slides). All slides were examined by an experienced pathologist (co-authors S.O. and H.M.). The pathological diagnoses and analyses were made according to the fourth edition of *The General Rules for the Clinical and Pathological Study of Primary Liver Cancer*, published by the Liver Cancer Study Group of Japan [17].

Statistical analysis

A statistical comparison of survival after LT was performed using the Kaplan-Meier method and compared by the log-rank test. Results were considered statistically significant when the *P* values were less than 0.05.

Results

At the time of LDLT, there was no sign of extrahepatic cancer spread in any of the patients. Histologically, after pre-LT therapy, viable HCCs were still observed in 9 (47%) out of 19 "thought-to-be necrotic" lesions (Fig. 2). The median period between pre-therapy and LT was 22 months (range 3–58 months). In 3 lesions, residual HCCs were found in the area next to necrotic area (Fig. 3), while in 6 lesions, residual HCCs were found within the same nodule (Fig. 4). With regard to tumor differentiation, there was no sarcomatous HCC in the treated residual lesions. No "forced" portal venous tumor thrombus was found around the remaining viable HCCs.

After LDLT, no recurrence was found except for one peritoneal dissemination (1/18:5.5%) after OLT. Since the type of recurrence is unusual after OLT, this case report will be shown below.

In fact, there were three patients transplanted for HCC beyond Milan Criteria, two of which had undergone pre-LT therapy (Fig. 1). In one patient, HCC recurred in the lung

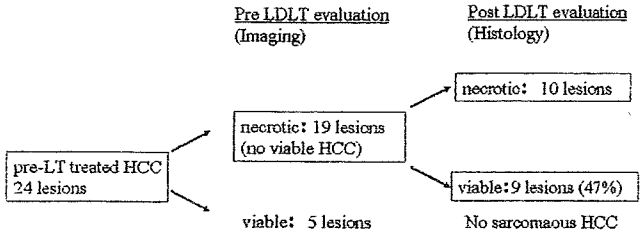

Fig. 2 Actual effect of pre-LT therapy on HCC. *LDLT* living donor liver transplantation, *HCC* hepatocellular carcinoma

12 months after LDLT, and he underwent partial lung resection three times. As pre-LT treatment, he had undergone liver resection and multiple TACE before LDLT. Another patient died at one month after LDLT due to hemophagocytic syndrome.

Survival after LDLT

After LT, regardless of pre-LT therapy, patient survival and recurrence-free survival were comparable between the groups (Fig. 5)

Case report

One patient underwent pre-LT treatments and subsequently developed peritoneal recurrence after LDLT. The patient was a 62-year-old male who had suffered from end-stage liver cirrhosis due to hepatitis C virus infection and was indicated for LDLT in May, 2006. Previously, he underwent a caudate lobe resection of the liver for HCC in 2001 and TACE for HCC in segments 4 and 7 in 2003. Subsequently, he was treated with TACE for HCC in segments 4 and 7 in 2004 and PEIT for HCC in segment 7 in 2004. RFA was a procedure of choice for an HCC in segment 2 in January, 2006. Finally, he developed end-stage liver failure and underwent a transplant in May, 2006. In the explanted liver, under WLHE, no viable HCCs were found.

However, following an increase in the AFP and PIVKA-II, two mass lesions were found in Douglas's pouch and the left lower abdomen in October, 2007. He had been on cyclosporine monotherapy as immunosuppression. Two lumpectomies were performed, which revealed moderately differentiated HCC under histological examination. It was presumed that the pre-LT treatment had disseminated the HCC, which developed slowly after the LDLT (Fig. 6). In August 2008, the patient died due to the multiple recurrence of HCC (local recurrence in the Douglas's pouch, bone metastasis, multiple liver metastases in the graft and multiple lung metastases).

Discussion

The present study demonstrated that after pre-LT therapy, 47% of the lesions still had viable HCC cells. Previously, Kim et al. [19] reported that a viable tumor volume ratio greater than 10% after pre-LT therapy was a significant prognostic factor. Pompili et al. [20] also reported that 58.7% of HCC had partial necrosis after percutaneous ablation procedures and the effect depended on the size of HCCs. Also, Wong et al. reported that fifteen nodules in five patients had <75% necrosis and these were due to

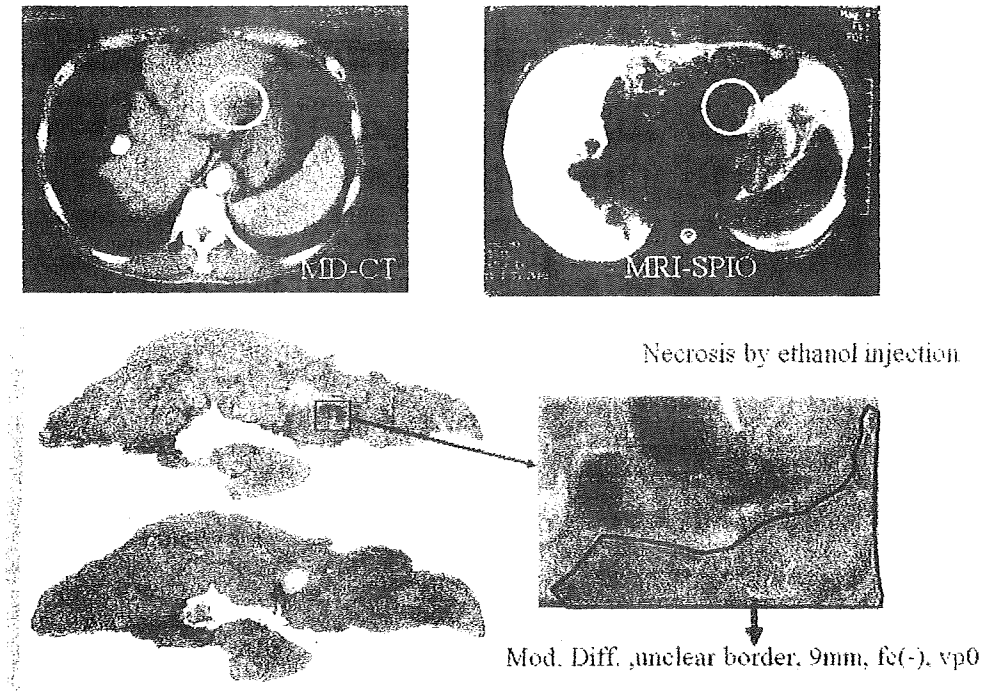

Fig. 3 A case presentation of a 58-year-old male. Liver cirrhosis due to hepatitis B viral infection, pre-LT imaging diagnosis: HCC 0

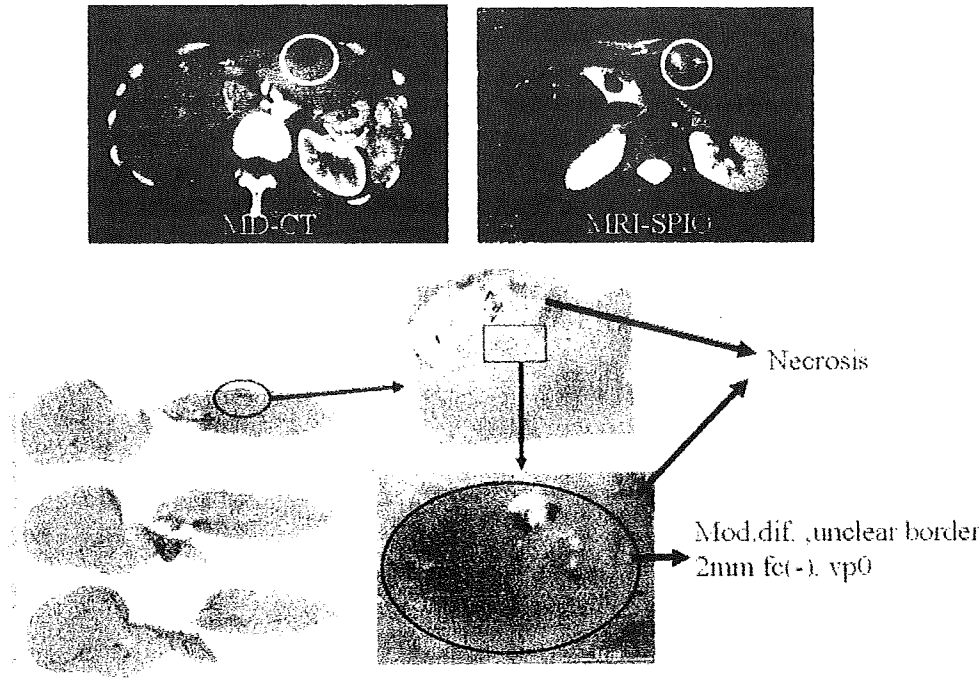

Fig. 4 A case presentation of a 33-year-old female. Liver cirrhosis due to hepatitis B viral infection, pre-LT imaging diagnosis: HCC 0

local/non-local recurrences or perhaps suboptimal treatment with RFA, TACE or cisplatin gel injection [21]. The mean waiting time for LT was 162.5 days. Nine of 13 patients had a different number of nodules than before pre-LT therapy, although stage changed in only three patients. The last pre-LT therapy and LDLT, which was median 11 months in our study, signified that salvage LDLT was considered and performed with 1 year for HCC bearing patients with viral hepatitis. Indeed, the outcome of LDLT even after at most pre-LT therapy, showed good disease-free-survival.

However, in the current study cohort, one case had peritoneal metastasis although PEI and RFA had been performed before LDLT. The patient finally died 2 years after LDLT with systemic metastases following resection

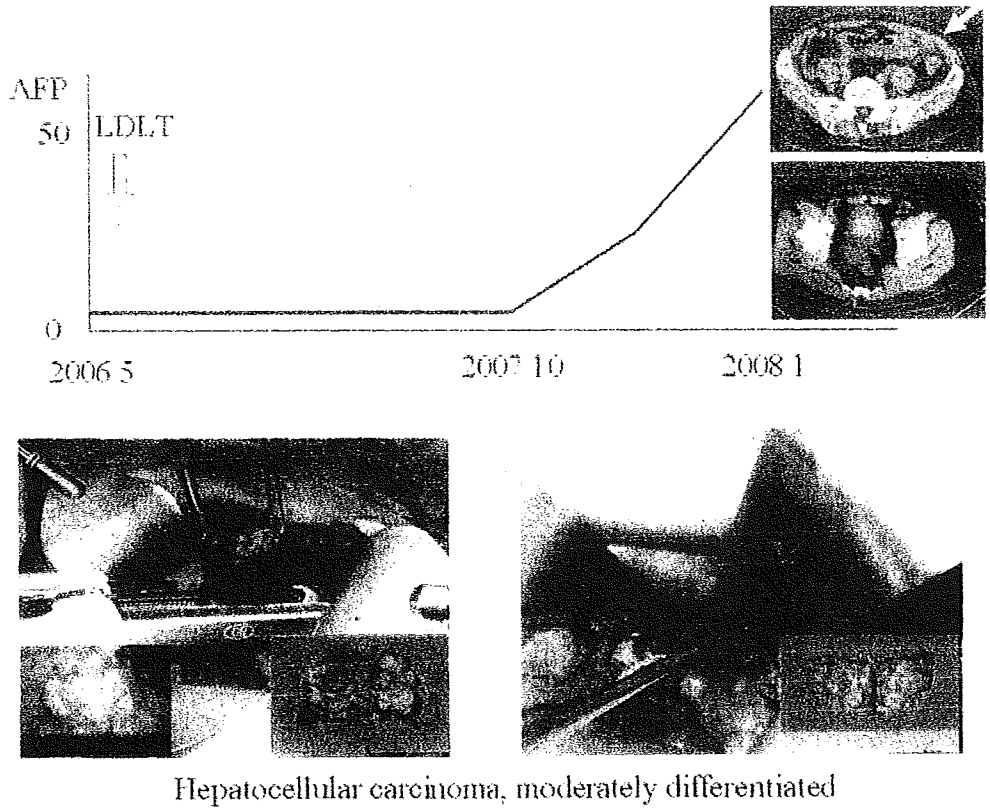

Fig. 5 A case presentation of peritoneal dissemination after LDLT. *LDLT* living donor liver transplantation

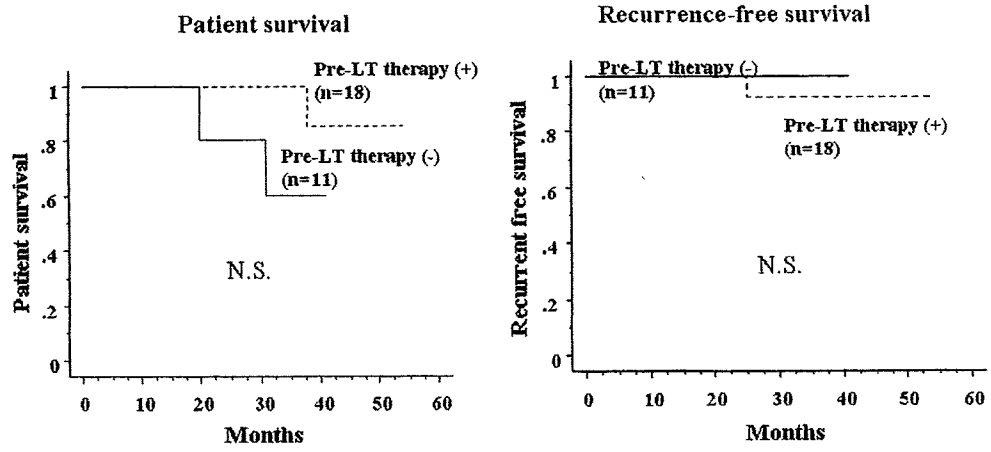

Fig. 6 Patient survival and recurrence-free survival after liver transplantation for patients with HCC within the Milan criteria

of 2 peritoneal metastases. In this case, there was no residual HCC in the explanted liver at the time of LDLT. This case illustrates a worst-case scenario with regard to pre-LT treatment for HCC. Therefore, physicians should keep in mind that percutaneous locoregional therapy for HCC might cause such micro-dissemination with subsequent growth under immunosuppressive therapy. The value of adjuvant chemotherapy and choice of immunosuppressive agent such as Rapamycin needs to be further determined [22]. Although previous reports on pre-LT therapy basically tend to favor the treatment, the case documented above suggested some detrimental effect of percutaneous therapy for HCC.

With regard to the recurrence-free survival after LT, there was no significant difference between the patients with or without pre-LT therapy. Recently, Yao et al. [23] reported that after downstaging with pre-LT therapy in 61 patients the 1- and 4-year survival after LT was 96.2 and 92.1% respectively. There was no recurrence after LT. Overall, the recurrence-free survival after LT in patients after pre-LT treatment was as good as in patients with T2 HCC without therapy for HCC. The study cohort in the

current review were patients who received previous treatment for HCC, namely salvage liver transplantation. In comparison to down-staged patients, salvage LT patients should have a better survival since those patients have never demonstrated a condition beyond the Milan-Criteria. Therefore, the current results showing a good disease-free survival after LDLT is warranted.

Since the purpose of this study is to investigate the pre-LT treated lesions, we did not relate much information on untreated HCC. Investigation of untreated HCC and occult HCC were described by us recently [16]. The characteristics of the occult HCCs that were undetectable by imaging, included a minute (median size 6 mm), well-differentiated appearance (80%), with indistinct margins (85.3%) and without vascular invasion (94%). In the study, a multicentric occurrence of HCCs was demonstrated in cirrhotic livers with HCCs within the Milan criteria, although undetectable HCCs in cirrhotic livers may have no impact on recurrence after LT.

In conclusion, after pre-OLT therapy, 47% of the lesions still had viable HCC cells. However, pre-LT therapy for HCC in salvage LT had no effect on the outcome of LT. However, one case had peritoneal recurrence probably due to percutaneous locoregional therapy under immunosuppression.

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Anatomy-Specific Pancreatic Stump Management to Reduce the Risk of Pancreatic Fistula After Pancreatic Head Resection

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Abstract
Background The anatomical status of the pancreatic remnant after a pancreatic head resection varies greatly among patients. The aim of the present study was to improve management of the pancreatic remnant for reducing pancreatic fistula after pancreatic head resection.
Methods Ninety-five consecutive patients who underwent an end-to-side, duct-to-mucosa pancreaticojejunostomy after pancreatic head resection were included in the study. To approximate the pancreatic stump to the jejunum, the transfixing and interrupted suture techniques were used in 51 and 44 patients, respectively. We modified the interrupted suture technique according to the anatomical status of the pancreatic remnant, i.e., the shape of the pancreatic stump and the location of the pancreatic duct.
Results There was no operative mortality in this study. Overall, 14 patients (15%) developed a clinically relevant pancreatic fistula. Certain anatomical features, including a small pancreatic duct, a soft, nonfibrotic pancreatic gland, and a pancreatic duct adjacent to the posterior cut edge, were significantly associated with pancreatic fistula. The fistula rate in the interrupted suture group was 7%, lower than that (22%) in the transfixing suture group ($P = 0.036$), and it was not influenced by pancreatic anatomy. Multivariate analysis identified a nonfibrotic pancreas (versus fibrotic pancreas; odds ratio [OR] 12.58, 95% CI 1.2–23.9; $P = 0.001$), a soft pancreas (versus hard pancreas; OR 4.67, CI 1.2–51.1; $P = 0.006$), and the transfixing suture technique (versus interrupted suture technique; OR 9.91, CI 1.7–57.5; $P = 0.003$) as significant predictors of clinically relevant pancreatic fistula.
Conclusions Pancreatic anastomosis modified according to the pancreatic anatomy is effective in reducing the risk of pancreatic fistula formation with end-to-side, duct-to-mucosa pancreaticojejunostomy after pancreatic head resection.

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Introduction

Significant advances in surgical technique and critical care management have substantially reduced the mortality associated with pancreatic surgery. However, morbidity remains considerably high, even in high-volume centers, approaching 40–50%, and pancreatic fistula still accounts for the majority of surgical complications following pancreatic head resection [1–4].

Various risk factors for pancreatic fistula after pancreatic head resection have been identified, including advanced age [5], duration of jaundice [6], creatinine clearance [6], ampullary disease [3, 4, 7, 8], prolonged operations [5, 7], and intraoperative blood loss [5–7]. The most generally accepted determinants of postoperative pancreatic fistula are the size of the pancreatic duct [3, 8–10] and the consistency of the pancreatic remnant [2, 5, 7, 9, 10]. Despite the more than 80 different methods of pancreaticoenteric anastomosis that have been proposed for the prevention of pancreatic fistula, management of the pancreatic remnant after pancreatic head resection still remains a challenge because of the lack of a gold standard for all patients [11].

The anatomical features of the stump of the pancreatic remnant after pancreatic head resection vary greatly among patients, making it difficult to perform a safe pancreaticoenteric anastomosis in the same manner for all patients. In this study of patients undergoing a pancreatic head resection, we examined in detail the anatomical status of the pancreatic stump, including the actual thickness and width of the gland and the location of the main pancreatic duct, as well as the pancreatic duct size and gland consistency. Then we evaluated the risk factors—including the remnant pancreatic anatomy—for postoperative pancreatic fistula. Moreover, we investigated the efficacy of modifying the pancreatic anastomosis technique according to the anatomical conditions of each pancreatic remnant to reduce the risk of pancreatic fistula development.

Patients and methods

A total of 95 consecutive patients who underwent an end-to-side, duct-to-mucosa pancreaticojejunostomy after pancreatic head resection, between January 2002 and August 2008, were included in the study (Table 1). There were 51 men and 44 women with a mean age of 69 (range: 38–86) years. Pancreatic head resection was achieved by a pylorus-preserving pancreaticoduodenectomy (PPPD; $n = 66$), standard pancreaticoduodenectomy (PD; $n = 15$), pancreatic head resection with segmental duodenectomy (PHRSD; $n = 9$), or duodenum-preserving total pancreas head resection (DPPHR; $n = 5$). The pathological conditions leading to treatment included intraductal papillary mucinous neoplasms of the pancreas ($n = 29$), pancreatic ductal adenocarcinomas ($n = 27$), bile duct carcinomas ($n = 21$), ampullary carcinomas ($n = 7$), chronic pancreatitis ($n = 4$), pancreatic endocrine tumors ($n = 2$), solid pseudopapillary tumors of the pancreas ($n = 2$), gallbladder carcinomas ($n = 2$), and gastric carcinoma ($n = 1$).

Surgical procedures of pancreaticojejunostomy

Pancreaticojejunostomy was achieved by a double-layer method in all patients, 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. To construct the duct-to-mucosa anastomosis, a small incision with the same diameter as the pancreatic duct was made on the antimesenteric side of the jejunal limb, and anastomosis was performed between the pancreatic duct and the entire jejunal wall, with 6–10 interrupted sutures using a 5-0 or 6-0 polydioxanone stitch (PDSII; Ethicon, Inc, Somerville, NJ, USA). For approximating the pancreatic stump to the jejunum, the transfixing suture technique described by Kakita et al. [12] as "one-layer suturing" was used in 51 patients, with 6–8 sutures using a 4-0 polypropylene stitch (Prolene; Ethicon, Inc, Somerville, NJ, USA), whereas the interrupted suture technique was employed in the remaining 44 patients, with 12–16 sutures using a 4-0 Prolene stitch.

In the transfixing suture technique, the sutures for the outer layer were inserted from the anterior surface of the pancreatic remnant and introduced straight through the pancreatic parenchyma to the posterior surface (Fig. 1). The sutures then lifted the seromuscular layer of the jejunum widely enough to cover the pancreatic stump [12]. In the interrupted suture technique, the manner of outer-layer suturing was modified according to the anatomical status of the pancreatic remnant—i.e., the shape of the pancreatic stump and the location of the pancreatic duct (Fig. 2)—to achieve a tension-free approximation and also leave no

Table 1 Indication for pancreatic head resection

Indication	No. of patients	Type of surgery			
		PPPD	PD	PHRSD	DPPHR
Intraductal papillary mucinous neoplasm of the pancreas	29	15	3	7	4
Pancreatic ductal adenocarcinoma	27	19	8	0	0
Bile duct carcinoma	21	20	1	0	0
Ampullary carcinoma	7	5	1	1	0
Chronic pancreatitis	4	4	0	0	0
Endocrine tumor of the pancreas	2	0	0	1	1
Solid pseudopapillary tumor of the pancreas	2	2	0	0	0
Gallbladder carcinoma	2	1	1	0	0
Gastric carcinoma	1	0	1	0	0

PPPD pylorus-preserving pancreaticoduodenectomy, *PD* pancreaticoduodenectomy, *PHRSD* pancreatic head resection with segmental duodenectomy, *DPPHD* duodenum-preserving total pancreas head resection

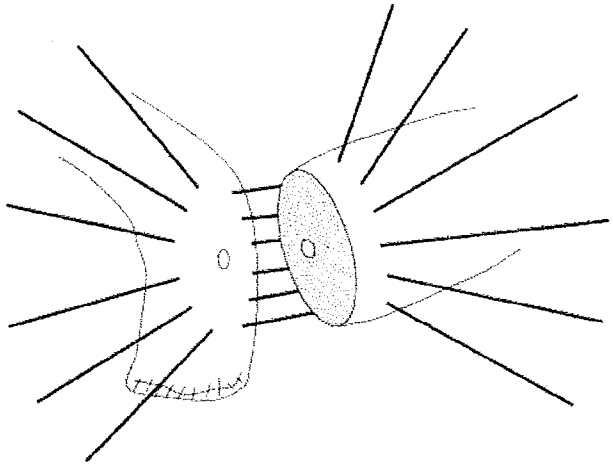

Fig. 1 The transfixing suture technique for pancreaticojejunostomy. The sutures for the outer layer are inserted from the anterior surface of the pancreatic remnant, introduced straight through the pancreatic parenchyma to the posterior surface, and then lifted the seromuscular layer of the jejunum

dead space between the pancreatic stump and the jejunal wall. In patients with a round or oval pancreatic stump ($n = 13$), the sutures were arranged circumferentially around the pancreatic duct in a radial fashion (Fig. 3a), such that the stitches were inserted from the pancreatic cut surface close to the inner suture line and introduced to the posterior surface for the posterior outer row of sutures, beginning at the posterior corner. For the placement of the anterior outer row of sutures, the stitches were inserted from the anterior pancreatic capsule and introduced close to the inner suture line. The sutures then picked up the seromuscular layer of the jejunum with the same radial arrangement (Fig. 3b). In patients with a flat pancreatic stump ($n = 31$), the sutures were placed perpendicular to the major axis of the pancreatic stump, with a parallel arrangement of sutures for both the anterior and posterior rows (Fig. 4). If the pancreatic duct was located close to the posterior cut edge of the pancreatic stump within a distance of 4 mm ($n = 24$), the first and second stitches for the posterior outer row of sutures were inserted close to the cephalic and caudal corner of the inner suture line, regardless of the shape of the pancreatic stump, and then penetrated to the posterior surface just below the pancreatic duct (Fig. 5).

The pancreaticojejunostomy was performed by five different surgeons, two with more than 15 years of surgical practice and three with less than 15 years of surgical practice. An external pancreatic duct stent was placed in 61 patients. No sealants were employed in any patients. Two drains were routinely placed close to the ventral side of pancreatic anastomosis for peritoneal drainage in each patient.

Detailed data recording

Preoperative data obtained included age; gender; history of jaundice; serum levels of albumin, total bilirubin and

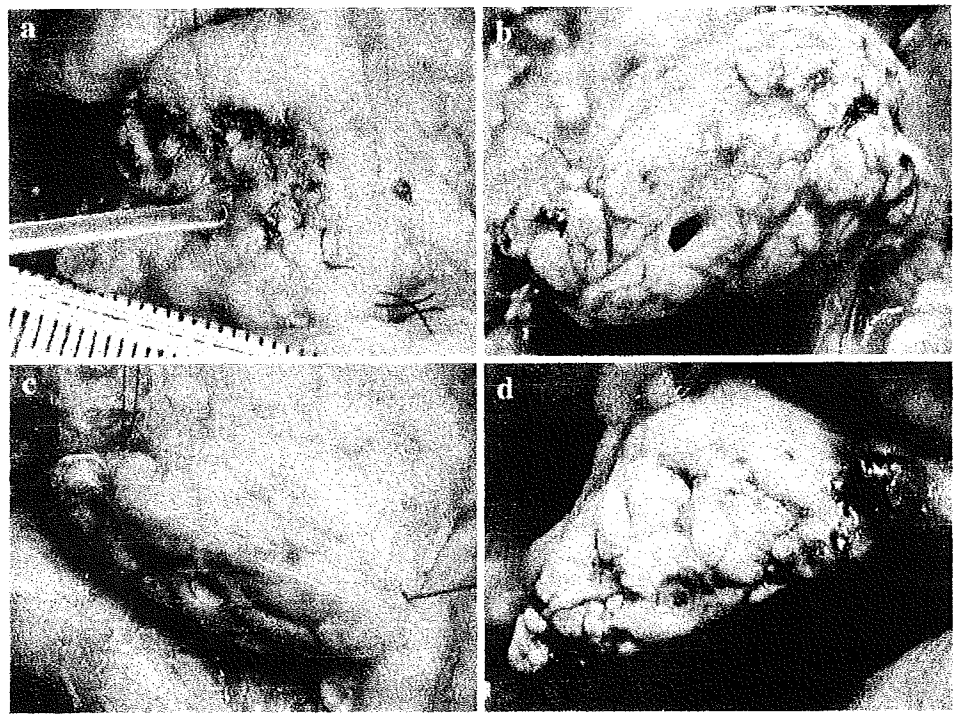

Fig. 2 Anatomical variation of the pancreatic stump:
(**a**) a round pancreatic stump,
(**b**) an oval pancreatic stump,
(**c**) a flat pancreatic stump,
(**d**) a pancreatic duct adjacent to the posterior cut edge

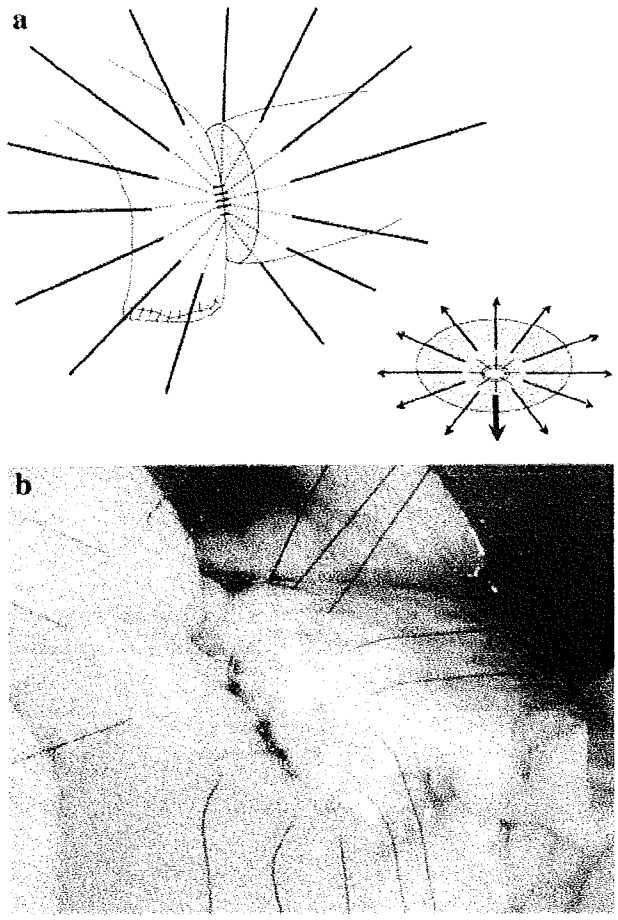

Fig. 3 The interrupted suture technique for pancreaticojejunostomy in patients with a round or an oval pancreatic stump. **a** The outer row of sutures is arranged circumferentially around the pancreatic duct in a radial fashion. **b** Anterior outer row of sutures between the pancreatic stump and the jejunal seromuscular layer in a patient with an oval pancreatic stump

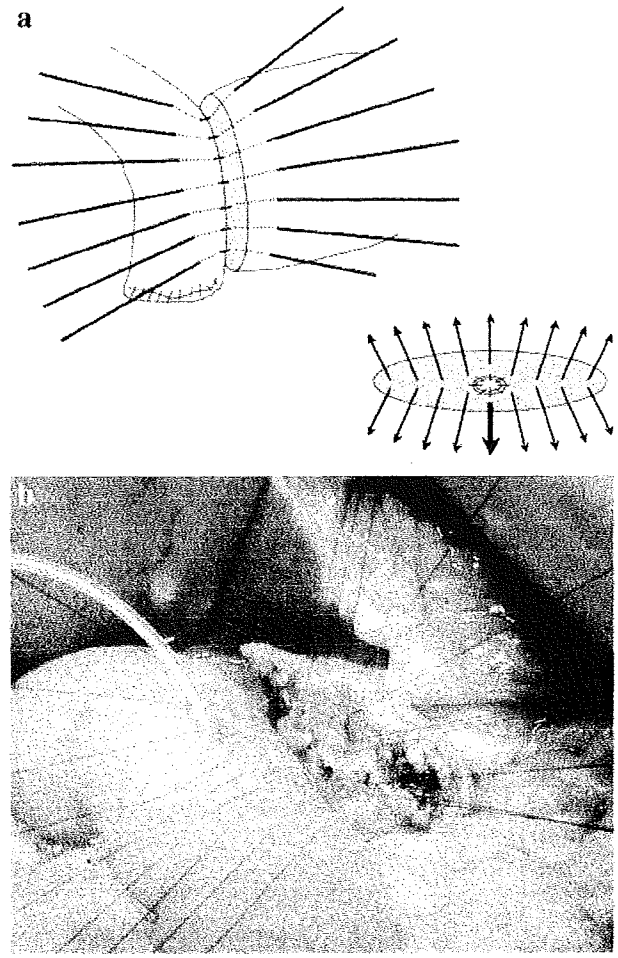

Fig. 4 The interrupted suture technique for pancreaticojejunostomy in patients with a flat pancreatic stump. **a** The outer row of sutures is placed perpendicularly to the major axis of the pancreatic stump in a parallel fashion. **b** Posterior outer row of sutures between the pancreatic stump and the jejunal seromuscular layer in a patient with a flat pancreatic stump

haemoglobin; lymphocyte counts; creatinine clearance; oral glucose tolerance test (OGTT); hemoglobin A1c (HbA1c) levels; *N*-benzoyl-L-tyrosyl-*p*-aminobenzoic acid (BT-PABA) test; profiles of the time-signal intensity curve (TIC) of the pancreas on dynamic contrast-enhanced magnetic resonance imaging (MRI); and primary disease pathology. Pancreatic TICs were obtained prior to surgery with a 1.5-T superconducting MRI system with the region of interest placed at the proposed transection line for the pancreas and were classified into three types: type I, characterized by a rapid rise to a peak followed by a rapid decline, indicating a normal pancreas without fibrosis; and types II and III with a slow rise to a peak followed by a slow decline or plateau, indicating a fibrotic pancreas [13].

The intraoperative variables included texture of the pancreatic gland, diameter of the pancreatic duct ($\leq$3 mm, >3 mm), thickness and width of the pancreas measured at the pancreatic stump, location of the pancreatic duct, type of pancreatic resection (PPPD, PD, PHRSD, or DPPHR), lymphadenectomy (none, regional, or extended), the outer-layer suturing technique for a pancreaticojejunostomy (transfixing suture or interrupted suture), use of a pancreatic stent, operative time, intraoperative blood loss, blood transfusion (with or without), and surgeon experience (<15 years, $\geq$15 years). The texture of the pancreas at the pancreatic stump was classified by the operating surgeon as soft (normal, friable), intermediate, or hard (fibrotic, sclerotic). The location of the pancreatic duct was evaluated at the pancreatic cut end by measuring the distance between the pancreatic duct and the cut edge of the pancreas in four directions: i.e., toward the anterior, posterior, superior, and inferior cut edges (Fig. 6).

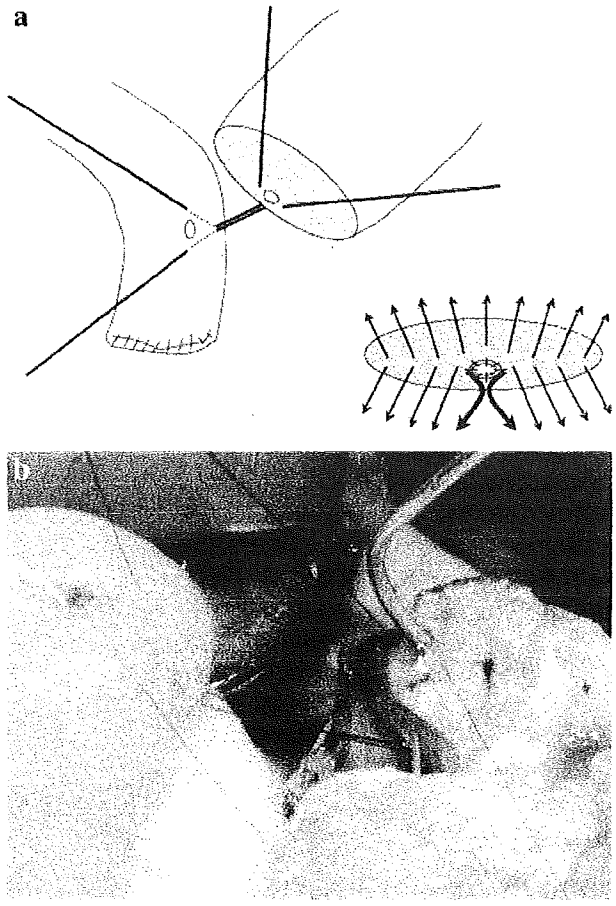

Fig. 5 The interrupted suture technique for pancreaticojejunostomy in patients with a pancreatic duct close to the posterior cut edge of the pancreatic stump (**a**). The first and second stitches for the posterior outer row of interrupted sutures in a patient with a pancreatic duct adjacent to the posterior cut edge (**b**). The stitches are inserted from the pancreatic cut surface close to the cephalic and caudal corner of the proposed inner suture line, and then penetrate to the posterior surface of the pancreas just below the pancreatic duct. A sonde is placed in the main pancreatic duct

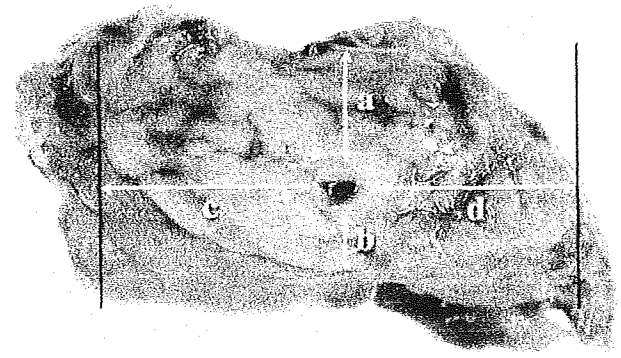

Fig. 6 Distance measurement between the pancreatic duct and the cut edge of the pancreatic remnant in the direction of the (**a**) anterior, (**b**) posterior, (**c**) superior, and (**d**) inferior cut edges

Study end point

The end point of the primary study was postoperative pancreatic fistula. Based on the International Study Group for Pancreatic Fistula (ISGPF) clinical criteria [14], pancreatic fistula was defined by the output via an operatively placed drain of any measurable volume of fluid on or after postoperative day 5, associated with an elevated amylase content greater than three times the upper limit of the normal serum amylase value (>390 IU/l). The severity of pancreatic fistula was classified into three grades as follows: grade A fistulas are transient, asymptomatic fistulas with only elevated drain amylase levels, for which treatments or deviation in clinical management are not required; grade B fistulas are clinically apparent, symptomatic fistulas that require diagnostic evaluation and therapeutic management; and grade C fistulas are severe, clinically significant fistulas that require major deviations in clinical management and aggressive therapeutic interventions.

Statistical analyses

In strict accordance with the ISGPF classification scheme, the patients were divided into two groups, as patients who lacked clinical evidence of fistula (no fistula or grade A fistula) and patients with a clinically relevant pancreatic fistula (grade B or C). The aforementioned 13 preoperative and 13 intraoperative parameters were registered as presumed risk factors for pancreatic fistula. To identify the variables associated with pancreatic fistula, the groups were initially compared using standard univariate statistical tests (chi-square test, two-tailed Fisher's exact test, and Mann–Whitney *U*-test, where appropriate). Statistically significant variables were then entered into a multivariable logistic regression analysis to assess any independent influences on postoperative pancreatic fistula. Values of $P < 0.05$ were considered to be statistically significant. All confidence intervals (CI) were at the 95% level.

Results

Morbidity and mortality

There was no operative deaths in this study. Pancreatic fistula of any extent occurred in 20 of the 95 patients (21%): 6 grade A fistulas, 12 grade B fistulas, and 2 grade C fistulas, presenting with a clinically relevant fistula rate of 15%. Two patients with a grade C fistula required surgical re-exploration for definitive management of the

problem. Other major postoperative complications included pulmonary complications (16%), delayed gastric emptying (7%), wound infection (6%), ascending cholangitis (4%), intra-abdominal abscess (3%), and biliary leakage (3%).

Risk factors

A comparison of perioperative risk factors for the two study groups is shown in Table 2. Among the 13 preoperative parameters, the BT-PABA test result ($P = 0.032$) and pancreatic TIC profile from dynamic MRI ($P < 0.001$) were significant predictors of a clinically relevant fistula in univariate analyses. Patients with normal exocrine pancreatic function were likely to develop pancreatic fistula. Of the 66 patients with type I pancreatic TIC, 14 (21%) demonstrated a clinically relevant pancreatic fistula, whereas none of the 29 patients with type II or III pancreatic TIC displayed pancreatic fistula. No significant differences in patient age, gender, history of jaundice, or laboratory values—including the concentrations of serum albumin, total bilirubin, and haemoglobin—lymphocyte counts, and creatinine clearance were noted between the two patient groups. The results of OGTT and HbA1c measurement had no impact on the occurrence of pancreatic fistula. Although a high rate of fistula was recognized in patients with bile duct carcinoma (19%), in comparison to patients with pancreatic ductal adenocarcinoma (7%) or chronic pancreatitis (0%), no significant differences in pathology were observed between the two patient groups.

Among the 13 intraoperative parameters, the texture of the pancreas ($P = 0.035$), pancreatic duct size ($P = 0.023$), location of the pancreatic duct (the distance between the pancreatic duct and the posterior cut edge of the pancreas; $P = 0.041$), and the surgical procedure of pancreaticojejunostomy ($P = 0.037$) were shown to be significant predictors of clinically relevant pancreatic fistula in univariate analyses. Patients with a soft pancreas or a small pancreatic duct (≤3 mm) were at extremely high risk for developing pancreatic fistula. Interestingly, patients with a pancreatic duct located close to the posterior edge of the pancreatic stump were likely to develop pancreatic fistula, regardless of the thickness and width of the pancreas, and in the present series, 9 of the 37 patients (24%) with such contiguity of the pancreatic duct to the posterior cut edge (≤3 mm) did develop pancreatic fistula. In contrast, 11 of the 51 patients (22%) who received the transfixing suture technique for the outer layer of pancreaticojejunostomy demonstrated a clinically relevant pancreatic fistula (9 grade B fistulas and 2 grade C fistulas). Meanwhile, the fistula rate related to the interrupted suture technique was 7% (3 grade B fistulas and no grade C fistulas). The type of pancreatic resection, the extent of lymphadenectomy, the operative time, intraoperative blood loss, the incidence of blood transfusion, and surgeon experience were similar for the two patient groups.

A multivariable logistic regression analysis of six factors univariately associated with pancreatic fistula—i.e., BT-PABA test, pancreatic TIC, texture of the pancreas, pancreatic duct size, location of the pancreatic duct, and anastomosis technique for pancreaticojejunostomy—identified pancreatic TIC (type I versus types II and III; odds ratio [OR] 12.58, 95% CI 1.2–23.9; $P = 0.001$), pancreatic gland consistency (soft versus hard; OR 4.67, CI 1.2–51.1; $P = 0.006$), and pancreaticojejunal anastomosis technique (transfixing suture versus interrupted suture; OR 9.91, CI 1.7–57.5; $P = 0.003$) as significant independent predictors of clinically relevant pancreatic fistula (Table 3).

A comparison of risk factors for pancreatic fistula between the transfixing suture group and the interrupted suture group is shown in Table 4. In the transfixing suture group, univariate analyses identified the occurrence of pancreatic fistula to be significantly influenced by the BT-PABA test result ($P = 0.033$), pancreatic TIC ($P = 0.001$), pancreatic texture ($P = 0.001$), pancreatic duct size ($P < 0.001$), and location of the pancreatic duct ($P = 0.001$). In the interrupted suture group, there were no significant risk factors predisposing a patient to postoperative pancreatic fistula.

Discussion

Pancreaticoenteric anastomosis still represents the "Achilles' heel" of pancreatic surgery [15]. In particular, pancreatic fistula is a leading cause of surgical complications after pancreatic head resection and is often linked with prolonged hospital stay, increased costs, and mortality [16–18]. The incidence of pancreatic fistula after pancreatic head resection reported in the literature ranges between 0% and 30% [1–4, 18–21]; however, the fistula rate strictly depends on the definition used [22]. In 2005, the ISGPF developed a universal definition of pancreatic fistula, with a grading system able to stratify complicated patients into three groups as grades A, B, and C, based on the clinical implications and costs of the postoperative course [14]. Grade A fistula presents with an elevated drain amylase level only, and it lacks any clinical consequences; i.e., it is a "biochemical" fistula. In contrast, grade B and C fistulas have an intermediate or a dramatic impact on patients, requiring therapeutic interventions. In this study, we evaluated the risks for pancreatic fistula after pancreatic head resection in two different study groups, patients who lacked clinical evidence of fistula (no fistula or grade A fistula) and patients with a clinically relevant pancreatic fistula (grade B or C fistula) in strict accordance with the ISGPF classification scheme.

Table 2 Univariate analysis of perioperative risk factors for clinically relevant pancreatic fistula following pancreatic head resection

Variables	Overall ($n = 95$)	Clinically relevant fistula ($n = 14$)	No fistula[a] ($n = 81$)	P Value
Age, years (mean ± SD)	68.9 ± 9.7	66.3 ± 9.8	69.4 ± 9.5	0.219
Gender				0.142
Male	51	10 (20)	41 (80)	
Female	44	4 (9)	40 (91)	
History of jaundice				0.723
Yes	31	4 (13)	27 (87)	
No	64	10 (16)	54 (84)	
Laboratory values				
Lymphocyte (1,000/mm^3)	2.0 ± 0.7	1.9 ± 0.4	2.0 ± 0.5	0.236
Hemoglobin (g/dl)	12.5 ± 07	12.8 ± 0.6	12.3 ± 0.4	0.581
Albumin (g/dl)	3.8 ± 0.8	3.7 ± 0.7	3.8 ± 0.6	0.769
Total bilirubin (mg/dl)	1.5 ± 1.9	1.6 ± 1.7	1.5 ± 1.4	0.734
Creatinine clearance (ml/min)	68 ± 20	66 ± 18	69 ± 16	0.292
Oral glucose tolerance test				0.334
Normal	43	8 (19)	35 (81)	
Impaired, diabetic	52	6 (12)	46 (88)	
Hemoglobin A1c (%)	5.8 ± 1.2	6.0 ± 1.5	5.6 ± 0.9	0.412
BT-PABA test (%)	60.7 ± 14.0	67.5 ± 12.9	59.5 ± 13.8	0.032
TIC of the pancreas				<0.001
Type I	66	14 (21)	52 (79)	
Type II, III	29	0 (0)	29 (100)	
Pathology				0.291
IPMN	29	4 (14)	25 (86)	
Pancreatic ductal adenocarcinoma	27	2 (7)	25 (93)	
Bile duct carcinoma	21	4 (19)	17 (81)	
Ampullary carcinoma	7	1 (14)	6 (86)	
Chronic pancreatitis	4	0 (0)	4 (100)	
Others	7	3 (43)	4 (57)	
Texture of the pancreas				0.035
Soft	52	11 (21)	41 (79)	
Intermediate	22	2 (9)	20 (91)	
Hard	21	1 (5)	20 (95)	
Pancreatic duct size (mm)				0.023
≤3	57	12 (21)	45 (79)	
>3	38	2 (5)	36 (95)	
Thickness of the pancreas (mm)	16.5 ± 3.7	16.6 ± 3.8	16.3 ± 3.4	0.878
Width of the pancreas (mm)	28.1 ± 5.6	28.3 ± 6.3	27.9 ± 5.5	0.866
Location of the pancreatic duct				
Distance between the pancreatic duct and the cut edge of the pancreatic remnant (mm)				
To the anterior edge (**a**)	9.1 ± 2.6	10.3 ± 3.1	8.7 ± 2.4	0.121
To the posterior edge (**b**)	4.1 ± 1.7	3.3 ± 1.9	4.3 ± 1.7	0.041
To the superior Edge (**c**)	11.3 ± 3.5	11.4 ± 2.7	11.1 ± 3.5	0.838
To the inferior edge (**d**)	13.7 ± 9.5	14.1 ± 4.8	13.6 ± 4.9	0.791
To the posterior edge (**e**)				0.037
≤3 mm	37	9 (24)	28 (76)	
>3 mm	58	5 (9)	53 (91)	

Table 2 continued

Variables	Overall ($n = 95$)	Clinically relevant fistula ($n = 14$)	No fistula[a] ($n = 81$)	P Value
Type of pancreatic resection				0.571
PPPD	66	10 (15)	56 (85)	
PD	15	3 (20)	12 (80)	
PHRSD	9	1 (11)	8 (89)	
DPPHR	5	0 (0)	5 (100)	
Lymphadenectomy				0.961
None	6	1 (17)	5 (83)	
Regional	30	4 (13)	26 (87)	
Extended	59	9 (15)	50 (85)	
Pancreaticojejunal anastomosis				0.036
Transfixing suture	51	11 (22)	40 (78)	
Interrupted suture	44	3 (7)	41 (93)	
Use of a pancreatic stent				0.209
Yes	61	11 (18)	50 (82)	
No	34	3 (9)	31 (91)	
Operative time (h)	8.3 ± 1.0	8.4 ± 1.5	8.3 ± 0.9	0.835
Blood loss (ml)	872 ± 287	864 ± 323	876 ± 223	0.661
Blood transfusion				0.989
With	27	4 (15)	23 (85)	
Without	68	10 (15)	58 (85)	
Surgeon experience				0.913
<15 years	26	4 (15)	22 (85)	
≥15 years	69	10 (14)	59 (86)	

Values in parentheses are percentages of row totals

BT-PABA N-benzoyl-L-tyrosyl-*p*-aminobenzoic acid, *TIC* time-signal intensity curve, *IPMN* intraductal papillary mucinous neoplasm of the pancreas

[a] Patients who lacked clinical evidence of fistula—no fistula or Grade A fistula

Pancreatic fistula of any extent occurred in 20 of the 95 pancreatic-head-resection patients (21%) in this study, and 14 (15%) of the fistula cases were clinically relevant. The BT-PABA test result, pancreatic TIC profile, pancreatic texture, pancreatic duct size, location of the pancreatic duct, and surgical procedure of pancreaticojejunostomy were shown to be significantly associated with clinically relevant pancreatic fistula. Multivariate analysis revealed that the pancreatic TIC, gland consistency, and pancreaticojejunal anastomosis technique were significant independent predictors of pancreatic fistula. All these risk factors, except for the anastomosis technique, were pancreatic anatomy-related factors; both the BT-PABA test results and the pancreatic TIC profiles obtained from dynamic contrast-enhanced MRI well reflect the pancreatic anatomy, especially the degree of pancreatic fibrosis [13]. Patients undergoing pancreatic head resection have been categorized grossly into two groups based on the anatomical status of the pancreatic remnant: patients with a soft, fragile pancreas or small pancreatic duct, who are considered at high risk for pancreatic fistula, and patients with a fibrotic, firm pancreas, or dilated pancreatic duct, who are at low risk [2, 3, 5, 7–10, 23–25]. Our results mirrored these reported data.

A unique result of our analysis was that the location of the pancreatic duct had a significant impact on a patient's predisposition to develop a pancreatic fistula after pancreatic head resection. Within the body and tail of the pancreas, the pancreatic duct lies slightly cephalad to a line drawn midway between the superior and inferior edges of the pancreas, and the duct is also more posterior than anterior [26]. In our study group the average thickness of the pancreatic stump and that of the pancreatic parenchyma beneath the pancreatic duct were 16.5 mm and 4.1 mm, respectively. A pancreatic duct located close to the posterior cut edge within a distance of 3 mm, was a feature highly associated with pancreatic fistula, although neither the thickness/width of the pancreatic stump nor the distance between the pancreatic duct and the anterior, superior, or inferior cut edge of the pancreas had any effect on the development of pancreatic fistula. During double-layer

Table 3 Multivariate analysis of perioperative risk factors for clinically relevant pancreatic fistula following pancreatic head resection

Variables	Odds ratio for clinically relevant fistula	95% CI	*P* value
BT-PABA test (%)	1.04	0.9–1.1	0.204
TIC of the pancreas			
Type II, III	1	–	
Type I	12.58	1.2–23.9	0.001
Texture of the pancreas			
Hard	1	–	
Intermediate	1.26	0.7–6.3	0.982
Soft	4.67	1.2–51.1	0.006
Pancreatic duct size			
>3 mm	1	–	
≤3 mm	4.05	0.4–40.3	0.186
Distance between the pancreatic duct and the posterior cut edge of the pancreas			
>3 mm	1	–	
≤3 mm	1.31	0.2–7.0	0.748
Pancreaticojejunal anastomosis			
Interrupted suture	1	–	
Transfixing suture	9.91	1.7–57.5	0.003

95% CI 95% confidence intervals

Table 4 Univariate analysis of perioperative risk factors for clinically relevant pancreatic fistula following pancreatic head resection in comparison between the transfixing suture group and the interrupted suture group

Variable	Transfixing suture			Interrupted suture		
	Clinically relevant fistula ($n = 11$)	No fistula[a] ($n = 40$)	*P* value	Clinically relevant fistula ($n = 3$)	No fistula[a] ($n = 41$)	*P* value
BT-PABA test (%)	68.9 ± 14.1	58.5 ± 15.6	0.033	62.7 ± 7.5	60.4 ± 11.9	0.742
TIC of the pancreas			0.001			0.963
Type I	11 (31)	24 (69)		3 (10)	28 (90)	
Type II, III	0 (0)	16 (100)		0 (0)	13(100)	
Texture of the pancreas			0.001			0.628
Soft	9 (41)	13 (59)		2 (7)	28 (93)	
Intermediate	1 (6)	16 (94)		1 (20)	4 (80)	
Hard	1 (8)	11 (92)		0 (0)	9(100)	
Pancreatic duct size			< 0.001			0.309
≤3 mm	11 (37)	19 (63)		1 (4)	26 (96)	
>3 mm	0 (0)	21(100)		2 (12)	15 (88)	
Distance between the pancreatic duct and the posterior cut edge of the pancreas			0.001			0.079
≤3 mm	9 (45)	11 (55)		0 (0)	17(100)	
>3 mm	2 (6)	29 (94)		3 (12)	23 (88)	

Values in parentheses are percentages of row totals

[a] Patients who lacked clinical evidence of fistula—no fistula or Grade A fistula

pancreaticojejunal anastomosis, a duct-to-mucosa anastomosis can be safely applied even to a pancreatic duct adjacent to the posterior cut edge. However, such an anatomical situation would make more difficult a safe approximation between the pancreatic stump and the jejunal wall, especially in its posterior corner, and would likely result in pancreatic fistula.

Pancreatic stump management for reducing the risk of pancreatic fistula and subsequent septic complications after pancreatic head resection may involve some or all of the

following devices and procedures: the use of ultrasonically activated shears [27] or an ultrasonic dissector [28, 29] during pancreas transection, optimizing the blood supply to the pancreas [30], duct-to-mucosa pancreaticoenteric anastomosis [31–34], dunking pancreatojejunostomy [19, 25, 35], pancreaticogastrostomy [16, 25, 33, 36, 37], use of a pancreatic duct stent [38], omental wrapping of skeletonized major vessels [39, 40], or intraoperative octreotide administration via the gastroduodenal artery [41]. In the present study, we modified the outer-layer interrupted suture technique according to the anatomical status of each pancreatic remnant. As a consequence, a lower fistula rate of 7% was achieved in this group, compared to the transfixing suture group, which had a fistula rate of 22%. In addition, the fistula rate for the interrupted suture technique was the same, whether it was performed on a soft or a firm pancreas, a small or a large pancreatic duct, or even a pancreatic duct adjacent to the posterior cut edge. By contrast, the fistula rate was significantly influenced by the pancreatic anatomy in the transfixing suture group. Sugiyama et al. [28] examined four patients with a soft pancreas and a small main pancreatic duct and identified from 5 to 7 microscopic pancreatic ducts on the cut surface of the resected pancreas after a pancreaticoduodenectomy. We believe that the existence of branch pancreatic ducts that are exposed on the transected pancreatic surface can lead to pancreatic juice leakage and, ultimately, major anastomotic leakage after a pancreaticoduodenectomy. Thus the uniform transfixing suture technique, rather than the interrupted suture technique—which is tailored to the pancreatic anatomy—may therefore have limitations in preventing leaks from small side branches on the pancreatic cut surface, or it may even produce leaks from suture injury to the main pancreatic duct itself. Although a standardized single approach to pancreatic anastomosis may help to reduce operative morbidity after pancreatic head resection [42], it is reasonable to modify the pancreatic anastomosis depending on the diverse intraoperative pancreatic scenarios influenced by the anatomical features of the pancreatic stump from patient to patient. In performing a double-layer pancreaticojejunostomy, we generally recommend a radial arrangement of the outer-layer interrupted sutures around the pancreatic duct for a round or an oval pancreatic stump. In the case of a flat pancreatic stump, we used a parallel arrangement of sutures perpendicular to the major axis of the stump. To achieve a close, safe approximation between the pancreatic stump and the jejunal wall in patients with a pancreatic duct adjacent to the posterior cut edge of the pancreatic stump, the first and second stitches for the posterior outer row of sutures should be placed close to the cephalic and caudal corner of the pancreatic duct, and then penetrated to the posterior surface just below the pancreatic duct.

In conclusion, the presence of a small pancreatic duct, a soft pancreatic gland without fibrosis, a high output of pancreatic juice, and a pancreatic duct adjacent to the posterior cut edge increases the risk that a clinically relevant pancreatic fistula will develop after a pancreatic head resection. Modification of the anastomosis technique for the approximation of the pancreatic stump to the jejunum according to the anatomical status of the pancreatic remnant is effective in reducing the fistula rate when performing an end-to-side, duct-to-mucosa pancreaticojejunostomy.

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