Adjuvant hepatic arterial infusion chemotherapy after resection for pancreatic cancer using coaxial catheter-port system compared with conventional system

Abstract

Purpose: Previous reports have shown the effectiveness of adjuvant hepatic arterial infusion chemotherapy (HAIC) in pancreatic cancer. However, percutaneous catheter placement is technically difficult after pancreatic surgery. The purpose of this study was to evaluate the feasibility and outcome of HAIC using a coaxial technique compared with conventional technique for postoperative pancreatic cancer.

Materials and Methods: 93 consecutive patients who received percutaneous catheter-port system placement after pancreatectomy were enrolled. In 58 patients from March 2006 to August 2010 (Group A), a conventional technique with a 5-Fr indwelling catheter was used, and, in 35 patients from September 2010 to September 2012 (Group B), a coaxial technique with a 2.7-Fr coaxial catheter was used.

Results: The overall technical success rates were 97.1% in Group B and 86.2% in Group A. In cases with arterial tortuousness and stenosis, the success rate was significantly higher in Group B (91.7% vs 53.8%; *P*=0.046). Fluoroscopic and total procedure times were significantly shorter in Group B: 14.7min *vs* 26.7min (*P*=0.001) and 64.8min *vs* 80.7min (*P*=0.0051), respectively. No differences were seen in the complication rate. The 1-year liver metastasis rates were 9.9% using the conventional system and 9.1% using the coaxial system (*P*=0.678). The overall median survival time was 44 months. There was no difference in the survival period between two systems (*P*=0.312).

Conclusions: The coaxial technique is useful for catheter placement after pancreatectomy, achieving a high success rate and reducing fluoroscopic and procedure times, while maintaining the safety and efficacy for adjuvant HAIC in pancreatic cancer.

Introduction

Pancreatic cancer shows an aggressive course and is one of the major causes of cancer death. Although surgery is the only curative treatment for pancreatic cancer, most cases have recurrence after resection [1,2]. The liver is the most common site of recurrence after surgery, with a rate of up to 92% [3–7]. Currently, systemic gemcitabine has been widely used for adjuvant chemotherapy. However, frequent early hepatic recurrence remains a problem. Two randomized trials, CONKO-01 and JSAP-002, reported that the 1-year disease-free survival rate in the adjuvant gemcitabine group was around 50%, and the initial hepatic recurrence rate was 30-36% [8-10].

Our preliminary reports have demonstrated promising results; postoperative hepatic arterial infusion chemotherapy (HAIC) combined with systemic gemcitabine prevented early hepatic recurrence and prolonged survival [11]. Several investigators have also shown the efficacy of HAIC for postoperative pancreatic cancer [12–18]. However, to date, adjuvant HAIC has not been globally accepted due to the limited evidence from small sample size studies. In addition, the technical difficulty of catheter implantation after pancreatic surgery could also be a deterrent.

Interventional catheter-port system placement has a high technical success rate of more than 90% in general cases, i.e., unresectable or postoperative liver cancers [19-22]. However, in patients after pancreatic surgery, catheter placement is occasionally difficult due to tortuousness and/or stenosis of the celiac and/or common hepatic arteries caused by highly invasive surgery with lymph node dissection or postoperative complications such as pancreatic fistula [23,24]. The conventional placement, in which a 5-Fr indwelling catheter is placed using a guide wire exchange technique has been widely used as the standard technique for the past 2 decades [19,20]. In 2006, a coaxial indwelling catheter-port system was introduced and several previous reports showed the usefulness in cases in which conventional placement was difficult, i.e. placement through the pancreaticoduodenal arcade via the superior mesenteric artery [25-27]. Due to several possible drawbacks of the coaxial system, including dislocation of the catheter, obstruction of the system, and a weak connection between the microcatheter and the port, this coaxial system had never been used as a primary choice before this study.

In our institution, adjuvant HAIC for pancreatic cancer has been performed since March 2006. The conventional technique was applied for catheter-port placement until August 2010. Due to technical difficulties for postoperative pancreatic cancer patients, as mentioned above, from September 2010, we changed to the coaxial technique for the primary placement strategy. The aims of this study were as follows: (1) to compare the technical success rates and procedure times between the conventional technique and the coaxial technique; and (2) to evaluate the complications during HAIC, the rate of development of liver metastases and the survival period in the coaxial system compared to the conventional system.

Materials and Methods

Study Outline

This retrospective study consisted of three parts (Fig. 1). In the first part, the technical success rate, the procedure time and fluoroscopic time were compared between the two catheter-port placement techniques; the conventional system placement technique was used from March 2006 to August 2010 (Group A), and the coaxial system placement technique was used from September 2010 to September 2012 (Group B). In the cases in which the conventional system placement failed, coaxial system placement was performed during the same session. Likewise, in the cases in which the coaxial system placement failed, conventional system placement was performed during the same session. In the second part, system-related complications during HAIC were compared between the two catheter-port systems that were finally placed. In the third part, the rates of development of liver metastases and the survival periods were assessed.

Patients

Ninety-three patients who had undergone curative surgery for pancreatic ductal adenocarcinoma between March 2006 and September 2012 at our institution were included in this study. The clinical features of all patients are given in Table 1. Forty-five patients had no history of anticancer treatment other than pancreatectomy, whereas 48 had received neoadjuvant chemoradiotherapy (50-54 Gy, at 2 Gy/fraction) combined with intravenous gemcitabine. Fifty-six patients had undergone pancreaticoduodenectomy, 7 had undergone total pancreatectomy, and 30 had undergone distal pancreatectomy.

After pancreatic surgery, an arterial catheter-port system was placed for HAIC by interventional techniques, using either the conventional system or the coaxial system. The mean time interval period from the pancreatic surgery to the catheter-port system placement was 42±30 days. On the angiography for catheter-port system placement, tortuousness and/or stenosis of the celiac and/or common hepatic arteries was seen in 25 of 93 patients (26.9%). These were defined as stenosis over 50% and/or tortuousness and bending over 90 degrees. This judgment was made by experienced interventional radiologists based on findings of the celiac digital subtraction angiography (DSA) in the anterior-posterior (AP) view. (A.H., T.T.). All patients received adjuvant chemotherapy of HAIC using 5-fluorouracil (5-FU) combined with intravenous gemcitabine. The technical success was defined as that an indwelling catheter was placed in the hepatic artery to deliver the drug into the whole liver. The institutional review board approved the treatment protocols.

Catheter placement

Conventional technique

Under local anesthesia, a 4-Fr sheath (Hanako Medical, Tokyo, Japan) was introduced via the femoral artery. Through the sheath, a 4-Fr angiographic catheter (Hanako Medical) was inserted. Before catheter placement, in cases in which the replaced hepatic arteries were present, they were embolized with fibered microcoils (Tornado, Cook, Bloomington, USA) or interlocking detachable coils (IDC, Boston Scientific Corporation, Marlborough, USA) to redistribute the entire hepatic arterial flow from multiple arteries to a single artery [20]. The right gastric and gastroduodenal arteries were also embolized, if present, to prevent chemo-agent distribution to the gastrointestinal tract. Through a 4-Fr catheter, a 2.5-Fr, 105-cm-long microcatheter (Renegade, Boston Scientific) was inserted into the peripheral branch of the hepatic artery or the gastroduodenal artery. A 0.018-inch, 205-cm stiff guide wire (Piolax Medical Devices) was inserted through the microcatheter. Then, the whole system, including the sheath, the angiographic catheter, and the microcatheter, was replaced by an anticoagulant-coated indwelling catheter, with a 5-Fr proximal shaft and a 2.7-Fr distal shaft (Anthron PU catheter, Toray Medical, Urayasu, Japan) (Fig. 2).

The catheter tip was inserted into the hepatic artery or the gastroduodenal artery (only in patients who had undergone distal pancreatectomy), and the handmade side hole was positioned at the common or proper hepatic artery. Finally, at the right inguinal region, a U-shaped subcutaneous tunnel was created up from the femoral artery puncture site. The proximal end of the catheter was connected to an implanted port (Selsite Port, Toray Medical) and embedded in the lower abdominal wall.

Coaxial technique

As in the conventional technique, the replaced hepatic, gastric and/or gastroduodenal arteries were embolized, if necessary, before catheter placement. Via the femoral artery, a 5-Fr anticoagulant-coated leading indwelling catheter (Piolax Medical Devices) was placed into the celiac artery without a sheath. Through the 5-Fr leading indwelling catheter, an anticoagulant-coated 2.7-Fr W-Spiral coaxial catheter (Piolax Medical Devices) that had a spiral tip-mounted nitinol coil with shape memory alloy was inserted. The coaxial catheter was introduced using an 0.018-inch flexible guide wire (AQUA VIII, Cordis, Miami, FL). The tip of the W-Spiral coaxial catheter was placed in the hepatic artery, and the handmade side hole was positioned at the common or proper hepatic artery. After the guide wire had been drawn out, the leading indwelling catheter was withdrawn into the abdominal aorta (Fig. 3, 4). A subcutaneous tunnel was made in a loop, and the proximal end of a 2.7-Fr coaxial catheter was connected first, after which a 5-Fr leading catheter was advanced over the 2.7-Fr catheter to an implanted port (Nipro catheter access P, Nipro Corporation, Osaka, Japan).

Treatment Schedule and Follow-up

The treatment schedule for adjuvant HAIC consisted of 5-FU administered at a dose of 1000 mg/m^2 weekly for 5 hours using a continuous infusion device (Dosi-Fuser 65H5, Toray Medical) for 3 weeks of a 4-week cycle. After the chemoinfusion, 2mL of heparin was injected into the catheter-port system. The administration of hepatic arterial chemoinfusion was limited to 3 cycles. Concurrent systemic full-dose gemcitabine (1000 mg/m^2) was combined on the same administration days (days 1, 8, and 15, every 4 weeks). To detect HAIC-related complications, DSA and CT arteriography via the catheter-port system and intravenous contrast-enhanced CT were conducted after each cycle of chemotherapy. After the planned HAIC had been completed, the port-catheter system was removed. Additional systemic gemcitabine was administered in 3 cycles. During the follow-up period after the adjuvant therapy, the patients underwent contrast-enhanced CT every 2 months.

Statistical analysis

Statistical analysis was performed using SPSS software (version 21.0; IBM, Armonk, NY). Demographic features and clinical details of the groups were compared using Student's *t*-test or the chi-square test. The outcomes in terms of the technical success rate of catheter placement and complications were also compared using the chi-square test. The outcomes in terms of fluoroscopic time and total procedure time by catheter placement technique were compared using the Mann-Whitney U test. The hepatic metastasis development rates and survival periods were calculated with the Kaplan-Meier method and compared using the log-rank test. Values of $p < 0.05$ were considered significant.

Results

Comparison of catheter-port placement techniques

The conventional technique was used in 58 patients (Group A), while the coaxial technique was used in 35 (Group B). Coil embolization before catheter placement was required in 48.3% of cases in Group A and 28.6% of cases in Group B. Tortuousness and/or stenosis of the celiac and/or common hepatic arteries was seen in 13 patients (22.4%) in Group A and 12 patients (34.3%) in Group B. There were no significant differences in these values. Regarding the surgical methods, pancreaticoduodenectomy or total pancreatectomy was performed in 60.3% of cases in Group A and 80.0% of cases in Group B. Neoadjuvant chemoradiotherapy was performed in 41.4% of cases in Group A and 68.6% of cases in Group B. There were significant differences in these values (Table 2).

The success rate of catheter placement tended to be higher in Group B than in Group A

(97.1% versus 86.2%, P=0.084). Six of 13 patients with tortuousness and/or stenosis of the celiac and/or common hepatic arteries failed in Group A (success rate, 53.8%), whereas 1 of 12 patients with those findings failed in Group B (success rate, 91.7%). There was a significant difference between these rates (P=0.046). In 8 patients in Group A, in whom the conventional technique had failed, the coaxial technique was applied. In 1 patient in Group B, in whom the coaxial technique had failed, the conventional technique was applied. Finally, in all patients in both groups, a catheter-port system was successfully placed. Fluoroscopic and total procedure times were 26.7 and 80.7 minutes, respectively in Group A, and 14.7 and 64.8 minutes, respectively, in Group B. Fluoroscopic and total procedure times were significantly shorter in Group B than in Group A (P=0.001 and 0.0051, respectively) (Table 3).

Complications

In 51 patients, the conventional system was implanted, and in 42 patients, the coaxial system was implanted. During HAIC, severe hepatic arterial stenosis occurred due to chemo-infusion in 15.7% of the conventional system and 16.7% of the coaxial system patients (P=0.898), in whom HAIC was stopped due to the risk of liver abscess. No hepatic arterial thrombosis was seen in both groups. Catheter dislocation occurred in 5.7% of conventional system and 9.5% of coaxial system cases. Wound infection around the implanted port was observed in 3.9% of conventional system and 2.4% of coaxial system cases. Port-catheter system occlusion was detected in 4.8% of coaxial system cases. There was no significant difference in the total complication rate between the two systems (Table 4). All patients who had catheter dislocation, wound infection, or system occlusion underwent re-intervention to repair these troubles or a new catheter-port system was placed, and they continued HAIC.

Treatment outcome

The estimated liver metastasis rates were 9.9% at 1 year and 22.6% at 3 years with the conventional system, compared to 9.1% at 1 year and 24.7% at 3 years with the coaxial system (P= 0.678). The overall median survival time was 44 months. The 1 year and 3 years survival rates were 94.1% and 50.3%, respectively, using the conventional system, while 95.2% and 58.5%, respectively, using the coaxial system. There were no significant differences between them (p= 0.312).

Discussion

It could be considered that occult liver metastases are potentially present in many resectable pancreatic cancer patients, and they may become clinically visible during the early postoperative period [4,7,28]. The current study that included 93 patients also demonstrated low hepatic recurrence rates of around 9.1-9.9% at 1 year and 22-24% at 3 years. The overall median survival time in a current study of 44 months were also outstanding compared with previous reports using adjuvant gemcitabine alone. The survival time of KONKO-001 and JSAP-02 were around 22 months [8,9].

A meta-analysis showed that fluoropyrimidine treatment including 5-FU was effective to combine with gemcitabine for unresectable pancreatic cancer [29]. The effectiveness of intra-arterial 5-FU for pancreatic cancer has been shown in several studies, with tumor response rates of around 70% [30,31]. A previous dose escalation phase I study showed intermittent intra-arterial 5-FU at a dose of 1000 mg/m^2 was tolerable with full-dose systemic gemcitabine [30].

In approximately 30% of patients, tortuousness and/or stenosis was found in celiac and/or hepatic arteries on angiography before catheter-port system implantation. This made it difficult to implant a catheter-port system after pancreatic surgery. The technical success rate was only 53.8% with the use of the conventional technique in cases with tortuous and/or stenotic celiac and/or hepatic arteries. The main reason for this technical failure was the difficulty of insertion of the indwelling catheter along a guide wire. To date, there has been no consensus relating to the techniques of catheter placement after pancreatic surgery, and this issue has never been examined. Kurosaki et al. and Ohigashi et al. inserted a catheter via the gastroduodenal artery under laparotomy [5,18], and Beger et al. and Morak et al. temporarily placed an angiographic catheter for only 5 days into the celiac artery without connecting a port [17,18]. Hayashibe et al. placed an indwelling catheter into the hepatic artery angiographically, but they selected cases without arterial stenosis as eligible for catheter placement [14]. Therefore, it is important to investigate an appropriate interventional technique of catheter placement after pancreatic surgery.

To the best of our knowledge, this is the first comparative study of the conventional system and the coaxial system. The coaxial technique achieved a higher technical success rate of 97.1%. Even in patients with tortuous and/or stenotic celiac and/or hepatic arteries, the success rate was 91.7%. The fluoroscopic time of the coaxial technique was around half that of the conventional technique (14 minutes versus 27 minutes). The connection of the coaxial catheter to the port was intricate and needed additional time. However, the total procedure time was shorter in the coaxial technique. In one case, in which the hepatic artery was arising from the superior mesenteric artery, the coaxial system could not be inserted because the spiral tip of the catheter stuck at the orifice of the hepatic artery.

The complication rates during HAIC were similar between the two systems. This means that the coaxial system is also feasible for adjuvant HAIC for 3 months, as well as the conventional system. Catheter dislocation could be prevented due to the spiral tip with the mounted nitinol coil. System obstruction was observed in two patients with the coaxial system, which could have been caused by the tiny inner catheter diameter. To prevent system obstruction, careful injection of heparin into the system after HAIC is needed. Since the HAIC protocol was limited to 3 months, long-term results were not evaluated.

Based on the results of this study, currently, we choose the coaxial system in cases with stenosis and/or tortuousness of the celiac and/or hepatic arteries. Transbrachial or transsubclavian approach would be also an option to overcome the arterial stenosis and/or tortuousness cases.

There are several limitations in this study. First, this was not a randomized, controlled study comparing the coaxial system and the conventional system; instead, it was a retrospective analysis of these two systems with different study periods. Second, the definition of tortuousness and/or stenosis of the celiac and/or common hepatic arteries in this study was vague because AP view did not show the arterial course in ventral-dorsal direction. Third, the study showed continuing promising results regarding the efficacy of adjuvant HAIC after pancreatic resection in 93 patients. However, to establish a higher level of evidence, a phase III trial to compare gemcitabine plus HAIC versus systemic gemcitabine alone is needed.

In conclusion, the coaxial technique is useful for catheter placement after pancreatectomy with tortuous and/or stenotic celiac and/or hepatic arteries. The complication rate in the coaxial system was similar to that of conventional systems.

All authors have no conflicts of interest and financial disclosures.

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TABLE 1: Baseline Characteristics of Patients

Characteristics	Value	
Age (year)		
Median (range)	67.0 (33-80)	
Gender, n (%)		
Male	51	(54.8)
Female	42	(45.2)
Pathological diagnosis, n (%)		
Pancreatic ductal adenocarcinoma	93	(100.0)
Surgical method, n (%)		
PD	56	(60.2)
TP	7	(7.5)
DP	30	(32.3)
Preoperative treatment, n (%)		
None	45	(48.4)
NACRT	48	(51.6)

Note- PD: pancreaticoduodenectomy, TP: total pancreatectomy,
DP: distal pancreatectomy, NACRT: neoadjuvant chemoradiotherapy

TABLE 2: Demographic features and clinical details: Difference between catheter-port placement technique

	Group A		Group B		p value
Patients, n	58		35		
Age					0.607
Median (range), y	66	(33-80)	65	(36-80)	
Gender, n (%)					0.071
Male	36	(62.1)	15	(42.9)	
Female	22	(37.9)	20	(57.1)	
Surgical method, n (%)					0.049
PD or TP	35	(60.3)	28	(80.0)	
DP	23	(39.7)	7	(20.0)	
Coil embolization, n (%)	28	(48.3)	10	(28.6)	0.061
Tortuous and/or stenosis of artery, n (%)	13	(22.4)	12	(34.3)	0.211
NACRT plus resection, n (%)	24	(41.4)	24	(68.6)	0.011

Note-PD: pancreaticoduodenectomy, TP: total pancreatectomy, DP: distal pancreatectomy, NACRT: neoadjuvant chemoradiotherapy

TABLE 3: Clinical outcomes by catheter-port placement technique

Results	Group A (n=58)	Group B (n=35)	p value
Over all technical success rates (%)	86.2	97.1	0.084
Technical success rates in cases with arterial tortuousness and stenosis (%)	53.8	91.7	0.046
Fluoroscopic time (min), average (range)	26.7 (6-79)	14.7 (4-42)	0.001
Total procedure time (min), average (range)	80.7 (30-195)	64.8 (28-161)	0.0051

TABLE 4: Complication rate during HAIC

Results	Conventional system (n=51)	Coaxial system (n=42)	p value
Hepatic arterial stenosis (%)	8 (15.7)	7 (16.7)	0.559
Catheter dislocation (%)	3 (5.7)	4 (9.5)	0.392
Wound infection (%)	2 (3.9)	1 (2.4)	0.573
Port-catheter system occlusion (%)	0 (0.0)	2 (4.8)	0.201

Figure legends

Fig.1 Flow of study participants

In the first part, the technical success rate and the procedure and fluoroscopic times were compared between the two catheter-port placement techniques (group A vs group B). In the second part, system-related complications during HAIC were compared between the two catheter-port systems that were finally placed (conventional system vs coaxial system). In the third part, the rates of development of liver metastases and the survival periods were assessed.

Fig.2 The schema of the conventional technique

A, A 4-Fr angiographic catheter is inserted via a 4-Fr sheath, and through the 4-Fr catheter, a 2.5-Fr microcatheter is inserted. A 0.018-inch stiff guide wire is inserted into a peripheral branch of the hepatic artery through the microcatheter.

B, The whole system, excluding the 0.018-inch stiff guide wire, is removed.

C, An anticoagulant-coated 5-Fr indwelling catheter is placed over the guide wire.

D, The indwelling catheter tip is inserted into the peripheral branch of the hepatic artery, and the side hole is positioned in the common hepatic artery.

Fig.3 The schema of the coaxial technique

A, A 5-Fr leading indwelling catheter is placed into the celiac artery without a sheath.

B, Through the leading indwelling catheter, a 2.7-Fr W-Spiral coaxial catheter is inserted. The coaxial catheter is introduced using a 0.018-inch flexible guide wire.

C, After the guide wire is drawn out, the leading indwelling catheter is withdrawn into the abdominal aorta.

D, The 2.7-Fr W-Spiral coaxial catheter is pushed up to make a loop in the aorta. The spiral tip-mounted nitinol coil of the coaxial catheter is in the right or left hepatic artery, and the side hole is positioned in the common hepatic artery.

Fig.4 Angiography before and after coaxial system placement

A. Celiac arteriography in a patient who underwent pancreaticoduodenectomy shows stenosis of the common hepatic artery (arrow).
B. A coaxial catheter is inserted through the stenotic common hepatic artery. The catheter tip is placed in the proper hepatic artery (black arrow), and the side hole is positioned in the common hepatic artery (arrowhead). The leading catheter is placed in the aorta (white arrow).
C. Celiac arteriography in a patient who underwent distal pancreatectomy shows stenosis of the celiac artery (white arrow) and tortuousness of the common hepatic artery (black arrows).

D. A coaxial catheter is inserted through the stenotic celiac artery and the tortuous common hepatic artery. The catheter tip is placed in the right hepatic artery (black arrow), and the side hole is positioned in the proper hepatic artery (arrowhead). The leading catheter is placed in the aorta (white arrow).