Table 2 Adverse events in phase I study ($n = 13$)

Grade	1	2	3	4	All grade (%)	Grade 3/4 (%)
Hematological						
Leukocytopenia	1	1	0	0	2 (15%)	0
Anemia	6	5	0	0	11 (84%)	0
Thrombocytopenia	5	5	1	0	11 (84%)	1 (8%)
Non-hematological						
Anorexia	5	6	0	0	11 (84%)	0
Nausea	4	6	0	0	10 (77%)	0
Vomiting	3	1	0	0	4 (31%)	0
Elevated total bilirubin	2	5	0	0	7 (54%)	0
Elevated AST	1	7	5	0	13 (100%)	5 (38%)
Elevated ALT	3	6	4	0	13 (100%)	4 (31%)
Elevated creatinine	0	0	0	0	0	0
Renal failure	0	0	0	0	0	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

The course of adverse events after TACE is shown in Table 4. The peak AST/ALT elevation most commonly occurred on day 2, and grade 3 or 4 AST elevation and ALT elevation were observed 1 week after TACE in 1 case (4%) each. Thrombocytopenia developed on day 3–5, and even though the rate was high (84%) 1 week later, it fell to 20% 1 month later.

Pharmacokinetics

Plasma concentration-time curves for intra-arterial infusion of CDDP at 65 mg/m^2 that are the RD in HAI without and with lipiodol are shown (Fig. 1). In all points, sample with lipiodol (TACE) is less than the total platinum concentration in comparison with sample without lipiodol (HAI). Free platinum concentration became under the limits of measurement at 6 h after infusion both. However, at 2 h after infusion, free platinum concentration with lipiodol (TACE) was higher than without lipiodol (HAI) (Fig. 2).

Response

According to RECIST criteria, CR did not occurred in any of the 25 patients, PR in six patients, SD in 18 patients, and PD in one patient; the response rate was 24%. With

Table 3 Adverse events according to dose level in all patients

	All grades			Grade 3/4		
	Level 1–2 ($n = 6$)	Level 3 ($n = 19$)	Total ($n = 25$)	Level 1–2 ($n = 6$)	Level 3 ($n = 19$)	Total ($n = 25$)
Hematological						
Leukocytopenia	1 (17%)	1 (5%)	2 (8%)	0	0	0
Anemia	5 (83%)	10 (53%)	15 (60%)	0	0	0
Thrombocytopenia	4 (67%)	17 (89%)	21 (84%)	1 (17%)	1 (5%)	2 (8%)
Non-hematological						
Anorexia	4 (67%)	17 (89%)	21 (84%)	0	0	0
Nausea	4 (67%)	16 (84%)	20 (80%)	0	0	0
Vomiting	1 (17%)	12 (63%)	13 (52%)	0	0	0
Elevated total bilirubin	3 (50%)	9 (47%)	12 (48%)	0	0	0
Elevated AST	6 (100%)	19 (100%)	25 (100%)	3 (50%)	8 (42%)	11 (44%)
Elevated ALT	6 (100%)	19 (100%)	25 (100%)	2 (33%)	9 (47%)	11 (44%)
Elevated creatinine	0	1 (5%)	1 (4%)	0	0	0
Renal failure	0	0	0	0	0	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 4 Recovery from adverse events of all patients

Time after TACE	All grades		Grade 3/4	
	7 days	30 days	7 days	30 days
Hematological				
Leukocytopenia	2 (8%)	3 (12%)	0	0
Anemia	8 (32%)	3 (12%)	0	0
Thrombocytopenia	21 (84%)	5 (20%)	0	0
Non-hematological				
Anorexia	6 (24%)	2 (8%)	0	0
Nausea	0	0	0	0
Vomiting	0	0	0	0
Elevated total bilirubin	3 (12%)	4 (16%)	0	0
Elevated AST	20 (80%)	5 (20%)	1 (4%)	0
Elevated ALT	22 (88%)	3 (12%)	1 (4%)	0
Elevated creatinine	0	1 (4%)	0	0
Renal failure	0	0	0	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TACE, transcatheter arterial chemoembolization.

respect to the RD patients ($n = 19$), CR did not occurred in any patients, PR in four patients, SD in 14 patients, and PD in one patient; the response rate was 21% (Table 5). If we regarded lipiodol accumulation lesions in tumors as being not viable or necrosis, and theses lesions were excluded from the tumor size, response rate was 76% (CR,10; PR,9; SD,5; PD,1).

In total, TACE using CDDP was enforced 67 times in 25 patients during this study. Serious adverse events were not common and suggest that TACE using CDDP is safe.

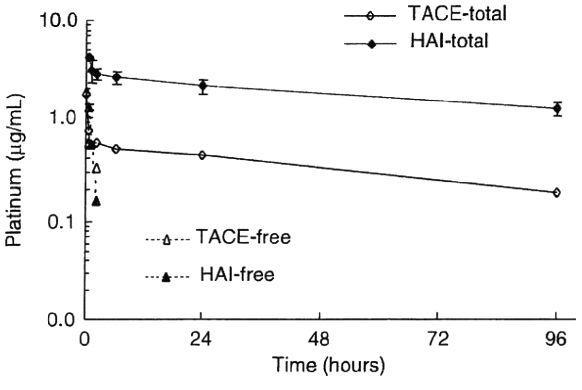

Figure 1 The concentration-time curves of total and free platinum in plasma. Cisplatin dose were 65 mg/m^2 both transcatheter arterial chemoembolization (TACE) with lipiodol, and hepatic arterial infusion (HAI) without lipiodol.

DISCUSSION

THIS PHASE I/II study demonstrated that fine-powder CDDP had a favorable safety and tolerability profile for patients with unresectable HCC who are treated with TACE. The dose 65 mg/m^2 can be recommended for future studies in Japanese patients with HCC. The response rate was 21%. There are no reports of the evaluation in RECIST in TACE using DXR or EPI. Therefore a phase II/III study with TACE using DXR or EPI for will be necessary.

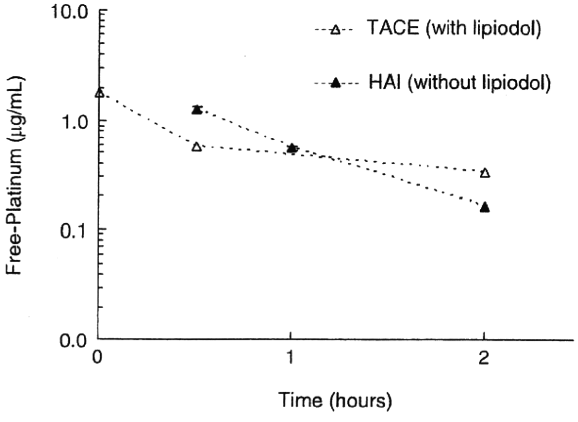

Figure 2 The concentration-time curves of free platinum in plasma. At 2 h after infusion, free platinum concentration with lipiodol (transcatheter arterial chemoembolization; TACE) was higher than without lipiodol (hepatic arterial infusion; HAI).

Table 5 Tumor response

	CR	PR	SD	PD	Response rate
All patients ($n = 25$)	0	6	18	1	24%
RD cases ($n = 19$)	0	4	14	1	21%

CR, complete response; PD, progressive disease; PR, partial response; RD, recommended dose; SD, stable disease.

CDDP is mainly excreted by kidneys, and its DLTs are nephrotoxicity, neurotoxicity, and hematologic toxicity.[11] Yoshikawa *et al.*[9] observed non-hematological toxicities (anorexia, vomiting, fever, general fatigue) in more than 30% of patients intra-arterially injected with fine-powder CDDP, and severe adverse events (grade 3 or higher) including anorexia (22.5%), vomiting (6.3%), and abdominal pain (1.3%). In addition, they reported grade 3 or higher thrombocytopenia (25.0%), neutropenia (13.0%), anemia (1.3%), AST/ALT elevation (11.3%), TB elevation (3.8%), and creatinine elevation (32.5%/2.5%). In this study, only grade 2 anorexia in four cases (21%) and vomiting in six cases (32%) were observed at the 65 mg/m^2 dose. In the present study, the incidence of grade 3 or more adverse events (expressed as % of all cases) was AST/ALT elevation (44) and thrombocytopenia (8) (Table 3). The reason for the lower rates of anemia, TB elevation, and creatinine elevation in their report appears to have been differences in the background characteristics of the eligible patients, and probably the differences in the plasma concentration platinum. On the other hand, the greater effect of embolization may account for the high rate of AST/ALT elevation.

The incidences of vomiting, thrombocytopenia, and anorexia tended to be higher at dose level 3 than at level 1–2. More specifically, vomiting was 17% at level 1–2, but increased to 63% at level 3. Thrombocytopenia and anorexia increased from 67% to 89%, respectively. Thus, caution should be exercised when the dose of CDDP is escalated (Table 3).

A separate phase I/II clinical study of TACE with a mixture of fine-powder CDDP and lipiodol was carried out by Yamashita *et al.* They reported an RD of 35 mg/m^2, and vomiting as the DLT.[12] In our study, the RD was 65 mg/m^2 even though TACE was performed using gelatin sponge particles and lipiodol. We think that the 5-HT$_3$ antagonist and steroid (administered by intravenous drip to every patient before TACE in our study) lowered the incidence of grade 3 vomiting.

The rate of response to fine-powder CDDP plus lipiodol (for all cases, 24%) was worse than the rate of response to fine-powder CDDP alone.[9] That is thought to be because lipiodol accumulates in and around the tumors and makes it difficult to accurately detect changes in tumor size on CT, and because all of the imaging evaluations were performed after one TACE session. Long-term follow-up of the efficacy of TACE with fine-powder CDDP seems to be necessary.

CDDP activity is concentration-dependent and time-dependent. Court *et al.* showed that the first-pass uptake of CDDP by tumors following intra-arterial delivery of 50 mg/m^2 at a rate of 1 mg/min to six HCC patients was 48.8% (range, 34.2–55%).[13] Therefore, CDDP should accumulate in liver tumors at even higher concentrations and have more therapeutic efficacy if CDDP is mixed with lipiodol and if injection is via the hepatic artery, both of which facilitate CDDP retention by the tumor.

In conclusion, TACE using gelatin sponge particles and lipiodol mixed with fine-powder CDDP at a dose of 65 mg/m^2 is well tolerated in patients with unresectable HCC.

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REVIEW

The technical advance and impact of caudate lobe venous reconstruction in left liver: additional safety for living-related donor liver transplantation

Shintaro Yamazaki,[1] Tadatoshi Takayama[1] and Masatoshi Makuuchi[2]

1 Department of Digestive Surgery, Nihon University School of Medicine, Itabashi-ku, Tokyo, Japan
2 Department of Hepato-biliary-pancreatic Surgery, Japanese Red Cross Medical Center, Shibuya-ku, Tokyo, Japan

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caudate lobe, hepatic vein reconstruction, living-related donor liver transplantation.

Correspondence
Tadatoshi Takayama MD, Department of Digestive Surgery, Nihon University School of Medicine, 30-1, Ohyaguchi kami-machi, Itabashi-ku, Tokyo 173-8610, Japan. Tel.: +81-3-3972-8111; fax: +81-3-3957-8299; e-mail: tadtak@med.nihon-u.ac.jp

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Summary

The key to obtaining good overall outcomes in small-for-size liver-graft transplantation is ensuring sufficient blood flow to the graft during the initial period after surgery. In left lobe liver grafting, various reconstruction techniques have been devised to maximize the limited graft volume. The reconstructions of the caudate lobe (CL) vessels were one of the main streams. In this article, we focus on the clinical significance of CL vessel reconstructions after small-for-size liver-graft transplantation and discuss the roles of various techniques. These techniques contribute to the enlargement of the margin of safety with respect to small-for-size liver-graft transplantation.

Introduction

Advances in surgical procedures and perioperative management have extended the application of small-for-size liver-graft transplantation. As a result, the number of small-sized liver grafts has been increasing. The criterion for the minimum graft size to adults has been defined as more than one-third in the ratio of the predicted graft volume/standard liver volume of the recipient. The graft volume and function together is an independent predictor of mortality during the early postoperative period [1]. While addressing this issue, performance of the concomitant caudate lobe (CL) resection has been a standard procedure for donor hepatectomy in marginal size graft. Left liver plus CL graft is a useful option for adult living-related donor liver transplantation (LDLT), because the addition of the CL can provide an 8–12% increase in graft weight [2].

Serious problems can affect grafts, especially in the initial few weeks after small-for-size liver-graft transplantation. Blood-vessel deformation and stenosis caused by rapid graft regeneration can be lethal [3]. One of the major challenges in LDLT is small vessels reconstruction in small-for-size liver grafts. Various reconstruction techniques have been devised to minimize vessel deformation and increase blood flow to the CL, to ensure full functioning of the graft. These techniques might increase the margin of safety for small-for-size liver-graft transplantation.

In this article, we summarized the advances made in the techniques and impact of CL venous reconstruction in left liver graft for increasing additional safety margin in living-donor-related liver transplantation.

Outflow reconstruction

Classical end-to-side direct anastomosis of a liver graft to the inferior vena cava (IVC) can cause twisting and deformation at the anastomotic site because of graft regeneration. This is significant in the first few weeks after surgery, when the caval window of the IVC is thin and the distance from the IVC is short [3]. End-to-end

anastomosis has been widely used to overcome this problem. A large orifice with two (left and middle hepatic veins) or three (left, middle, and right hepatic veins) major hepatic veins is commonly created at the recipient site [2]. Various reconstruction techniques (simple venoplasty, septoplasty, rectangular plasty, venoplasty with a vein graft patch, and creation of a wide circular cuff by vein grafting) are used depending on the grafted vessels [4–7].

In recent cases with a marginal predicted graft size relative to the recipient's metabolic demand, the short hepatic vein (SHV) was aggressively reconstructed [3,8]. Venous drainage from the CL occurred through the SHV and intraparenchymal communication. Good blood flow from other segments to the CL parenchyma might have facilitated graft growth. Without SHV reconstruction, the CL was often atrophied or regenerated slowly [9].

As reported in a previous study, the regeneration rates of the CL and other segments 1 month after LDLT without SHV reconstruction were 62 ± 24% and 152 ± 35%, respectively [10]. This was potentially attributable to insufficient venous drainage from the CL. By contrast, the regeneration rate of the CL with SHV reconstruction was greater than or equal to those of other segments. When the SHV was <3 mm in diameter or near the main hepatic vein, it had poor significance for reconstruction and the drainage domain was small. Caudate lobe regeneration was dependent on the tissue-perfusion area. In one study, a single SHV suitable for reconstruction was found in 22 out of 27 (81.5%) donors. The CL blood flow was classified according to the perfusion state as good (n = 15; 142.6 + 31.4%), fair (n = 7; 118.4 + 22.4%) or poor (n = 5; 90.1 + 36.5%) [9].

As shown in Fig. 1, the one-orifice technique simultaneously allows complete drainage of all veins, including the SHV, and minimal deformation of the outflow channel [7,11]. It can be used when there is a long distance between the IVC and SHV. The advantage of this method

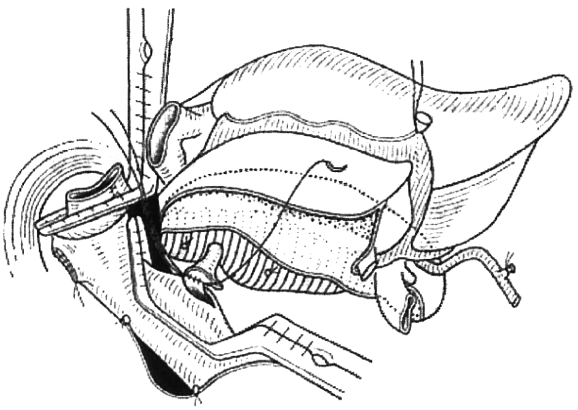

Figure 2 The conventional end-to-side direct anastomosis of the short hepatic vein to the inferior vena cava (IVC). Double outflow reconstructions were performed. (Main hepatic veins and short hepatic vein.) (Takayama *et al. J Am Coll Surg* 2000).

is that there were adequate suture margins between the IVC and the liver graft and single *in situ* vessel anastomosis. All intricate surgical procedures are performed on the back table, and a wide venous reservoir of the liver graft is simply attached end-to-end to the caval window. The vein graft functions as a circular cuff and conduit from the SHV. While it appears that the regeneration rate of the CL tends to be higher than that after conventional end-to-side SHV reconstructions (Fig. 2), this proposition needs further confirmation in more trials.

Inflow reconstruction

The isolated portal branch of CL is generally thin and not conventionally used in adult LDLT. An isolated portal branch of CL was found in 13.4% (9/67) of the donors, and 4.5% (3/67) of the cases were suitable for reconstruction [12].

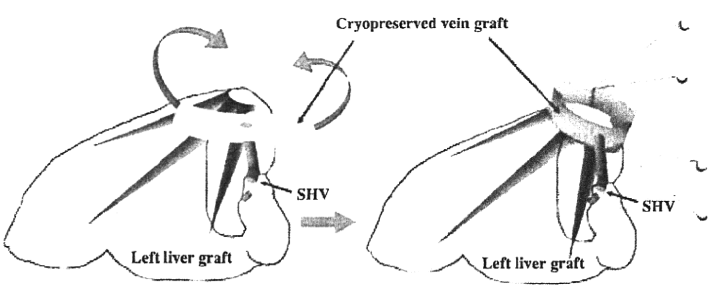

Figure 1 The one-orifice technique of the left liver graft. It allows complete drainage of all veins, including the SHV, and minimal deformation of the outflow channel. It can be used when there is a long distance between the inferior vena cava (IVC) and SHV. (Yamazaki *et al. Liver Transpl* 2009.)

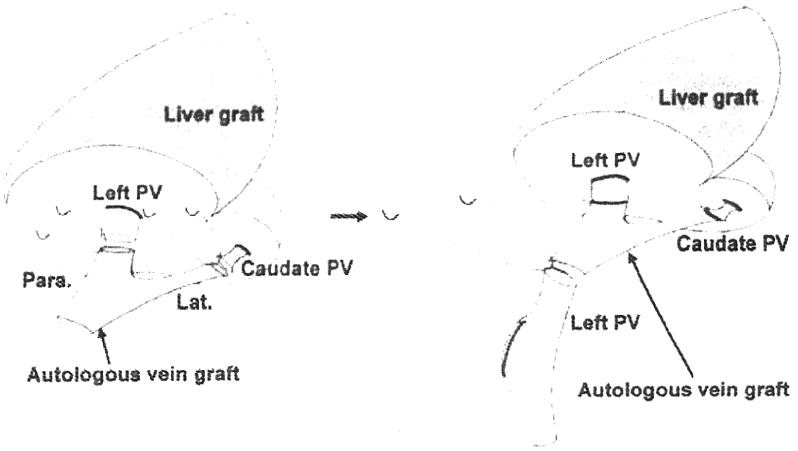

Figure 3 The autologous interposition methods of the portal vein (PV) reconstruction. The PV graft was extracted from the recipient's right PV branch together with the paramedian and lateral branches. The extracted autologous vein graft was interposed to the recipient's left PV branch in the back table. The lateral branch was sutured to the caudate PV and the paramedian branch was sutured to the left PV of the liver graft. (Yamazaki *et al. Liver Transpl* 2005.)

As reported in previous studies, an isolated portal branch of CL with a diameter <2 mm was considered to have poor significance for reconstruction, whereas CL inflow reconstruction was aggressively performed after small-for-size liver-graft transplantation when the diameter was >2 mm. The portal branch of CL was selected depending on the diameter and proximity to the left portal vein (PV) during graft harvesting. It was preserved with part of the recipient's PV like the Carrel's cuff. The recipient's autologous vein graft of the left PV with isolated portal branch of segment 1 or the right PV branches were used in most case (Fig. 3). The extracted PV together with the branches was interposed and extended [12,13]. Hence, inflow reconstruction may have a potential impact on small-for-size liver-graft transplantation.

Discussion

The graft-size mismatching is the most critical factor for success in LDLT while technical advances have enabled the use of relatively small-for-size grafts. The graft blood flow in the initial few weeks after surgery was reported to influence the overall outcome of small-for-size liver-graft transplantation [1]. Small-for-size grafts can experience problems relating to high PV pressure and high growth demands. Persistent PV hypertension and overperfusion in the initial few days after LDLT is the trigger of small-for-size syndrome (SFSS). Graft to recipient weight ratio of <1.0%, or <30% to 50% of standard/estimated liver volumes, have been used to define SFSS in previous studies [14,15]. The clinical manifestations of SFSS include delayed synthetic function followed by prolonged parenchymal damage of the liver. It also leads to prolonged cholestasis, coagulopathy, gastrointestinal bleeding, hyperbilirubinemia, and nonfunction or loss of the primary graft [16]. The pathogenesis of the SFSS is periportal injury in most cases. Whether the additional impact of the CL transplantation and revascularization contributes to the graft pressure gradients is unknown.

Although the CL volume is small, it is important when the graft volume is critical. Ikegami *et al.* have shown that the regeneration rate of the transplanted CL and other left lobe graft segments. The regeneration rate of the CL 1 month after transplantation was smaller (62 ± 24%) than that of other left lobe graft segments (152 ± 35%). With reconstruction of the inflow [12] or outflow [7], the regeneration rate of the CL was noted to be equal to or more than that of the other left lobe graft segments. The additional functional volume afforded by CL venous reconstruction might provide an additional safety margin.

As shown in Table. 1 various CL venous reconstruction techniques were devised as one of the feasible solutions to overcome the small-for-size graft. The CL outflow reconstruction is now widely performed and suitable for most left liver grafts. Direct anastomosis of the hepatic veins to a thin IVC can sometimes cause a bend at the anastomotic site, which results in outflow occlusion. The deformation of the outflow anastomosis caused by graft regeneration can lead to hepatic vein stenosis and graft congestion. This phenomenon is common when the outflow tract is narrow and the distance from the IVC is short. To overcome these problems, techniques for reconstructing hepatic vessels have been reported [8]. The CL regeneration rate might depend on the blood drainage to the reconstructed SHV. The width and length of the SHV are indicators of the adequacy of the blood flow. When

Table 1. The trends in the left liver plus caudate lobe venous reconstruction.

Author	Year	Reconstruction	Procedure
Miyagawa	1998	Without reconstruction	
Takayama	2000	Outflow	End-to-side
Ikegami	2001	Without reconstruction	
Sugawara	2002	Outflow	End-to-end
Kokudo	2004	Inflow	Autologous vein graft: recipient's left portal branch
Hwang	2004	Outflow	ND
Hashimoto	2005	Outflow	Cryopreserved vein graft wrapping
Yamazaki	2005	Inflow	Autologous vein graft: recipient's right portal branch

ND, not discussed.

the graft size is marginal with respect to the recipient's metabolic demand, outflow reconstruction of the SHV might have particular value. According to Couinaud's study, 69% (66/96) of CLs have a single vein and most of all the veins directly entered to the vena cava [17]. This result shows that the largest SHV reconstruction is the optimal method for outflow reconstruction.

To assure full graft viability and functioning, all of the feeding and drainage vessels for the CL should be reconstructed. However, it would be difficult to add inflow reconstruction of the portal branch of CL to the standard operation schedule, because it is possible in only <5% of all reported cases [12]. Inflow vascular reconstruction reportedly facilitates graft growth and small-for-size liver-graft transplantation; however, the operation time and liver-graft cold-preservation time on the back table are longer than those for procedures without revascularization. Recently, Kokudo *et al.* reported that the existence of isolated caudate PV was encountered in only 5.9% of 67 donors. Thereafter, only one case was reported about CL inflow reconstruction [13]. Thus, more results are needed to estimate the clinical value of caudate lobe PV reconstruction.

Inflow reconstruction thus is only of theoretical interest at present.

Complex venous reconstruction requires autologous and/or cryopreserved vein grafts, the use of which remains controversial. The main issues associated with cryopreserved vein grafts are the prolonged cold-ischemic time, underlying diseases, and graft shortages. The cryopreserved vein graft contains high rates of complications, such as aneurysm, thrombosis, and stricture of cryopreserved vascular grafts. Kuang *et al.* [18] report that six out of the seven vein grafts were complicated in a study published in 1996. Millis *et al.* [19] followed the report in pediatric patients, wherein 22 out of 42 patients (52%) encountered vein graft stenosis and thrombus. Recently, Sugawara *et al.* [20] reported that the preservation of integrity of patency of the cryopreserved vein graft used in transplant in 5 years was 58%. The complication rate of the cryopreserved vein graft is higher than that of autologous vein graft. Thus, the use of cryopreserved vein graft should be limited when autologous vein graft are available. Evidence of the larger outcomes is lacking and long-term follow-up remains necessary in this category of transplant recipients.

In conclusion, there is significant impact of the CL venous reconstruction in left liver graft. During liver harvesting, particular effort should be made to preserve the caudate branches in case of small-for-size liver grafting.

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Recent Advances in Chemotherapy for Advanced Gastric Cancer in Japan

MASASHI FUJII, MITSUGU KOCHI, and TADATOSHI TAKAYAMA

Department of Digestive Surgery, Nihon University School of Medicine, 1-8-13 Kandasurugadai, Chiyoda-ku, Tokyo 101-8309, Japan

Abstract
In the early 1990s, a combination of 5-fluorouracil (5-FU) and cisplatin was widely adopted to treat advanced gastric cancer; however, no survival advantage over single-agent 5-FU was confirmed by the results of randomized trials conducted over a long period. Recently developed agents such as irinotecan, taxanes (docetaxel), and new oral fluorouracil (S-1) have yielded more promising results, with a response rate of over 50% and a median survival time of over 10 months in combination studies. These newer combination regimens were investigated in various randomized phase III studies to clarify if the newer-generation regimens provided a survival advantage over the older-generation regimens. Based on the findings of a large randomized study, S-1 has become standard in the adjuvant setting after D2 dissection curatively resected stage II and III gastric cancer. This article reviews the recent advances in gastric cancer chemotherapy, especially in Japan.

Key words Gastric cancer · Chemotherapy · Standard chemotherapy

Introduction

Gastric cancer (GC) is the most common malignancy in Japan. In 1998, more than 100000 new cases were reported[1] and by 2015, it is anticipated that this number will have climbed to nearly 150000.[2] The only potentially curative treatment for GC is surgical resection of all of the gross and microscopic disease; however, recurrence is common, both in regional and distant sites. The standard treatment for advanced or relapsed gastric cancer (AGC) is chemotherapy, aimed at prolonging survival.

Until about 10 years ago, there were few medical oncologists in Japan, and gastrointestinal surgeons played the part of oncologists in designing cancer chemotherapy for patients with gastric or colorectal carcinomas. The educational systems for medical oncologists were initiated by the Japan Society of Medical Oncology (JSMO). However, from 2005 to 2007 only 205 specialists in medical oncology passed the JSMO examination. The JSMO predicts that 80 medical oncologists will be initiated into the system each year, but this will be insufficient to cover all patients who have AGC. Thus, surgeons must continue to treat their patients with AGC oncologically in Japan. Our aim in writing this review is to make surgeons aware of the widely used regimen or standard chemotherapy for GCs, because we expect them to be able to treat their AGC patients effectively and safely.

Anticancer Drugs for AGC

One of the most widely studied single-agent chemotherapies is the antimetabolite, 5-fluorouracil (5-FU), which confers response rates of approximately 20%.[3,4] Tumor antibiotics (mitomycin C, doxorubicin, and epirubicin), heavy metals (cisplatin and carboplatin), taxanes (paclitaxel and docetaxel), and camptothecins (irinotecan and topotecan) have also been evaluated in the treatment of AGC and afford response rates ranging from 5% to 30%.[5–7] Newer fluorinated pyrimidines such as the 5-FU prodrug, UFT (uracil and tegafur), and 5-FU derivatives such as S-1, are of particular interest since they can be administered orally and allow for mimicking of conventional infusional therapy.

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Is Chemotherapy Effective Against AGC?

Several combination chemotherapeutic regimens have been evaluated for their efficacy and tolerability in the treatment of AGC. They often achieve adequate response rates with variable toxicity in previously untreated AGC patients. Compared with the best supportive care, the median survival with combination chemotherapy appears to be increased by 2 months or longer.[8,9]

Standard Chemotherapy for AGC in Western Countries

In Western countries, FAM (5-FU/adriamycin/mitomycin C), FAMTX (5-FU/adriamycin/methotrexate), ELF (etoposide/leucovorin/5-FU), and CF (cisplatin/5-FU) regimens have been compared in several studies. In consideration of their moderate activity, we do not recommend that any of the evaluated regimens be regarded as the standard treatment. In a prospective, randomized phase III study, Waters et al.[10] compared a combination of epirubicin, cisplatin, and 5-FU (ECF) with FAMTX in previously untreated patients with AGC. This ECF regimen resulted in significantly higher response rates (46% vs 21%), median survival (8.7 vs 6.1 months), and 2-year survival rates (14% vs 5%), and is the de facto standard treatment for AGC in Europe.

In a randomized phase III study (TAX325), Moiseyenko et al.[11] compared the efficacy and safety of cisplatin and 5-FU (CF) vs docetaxel, cisplatin, and 5-FU (TCF) as front-line therapy in patients with metastatic or nonresectable AGC. The final analysis revealed that the addition of docetaxel to CF resulted in significantly higher response rates (37% vs 25%, for TCF and CF, respectively). Time-to-progression, the primary study endpoint, was significantly higher in the TCF-treated patients than in the CF-treated patients (5.6 months vs 3.7 months, respectively; $P < 0.0004$). At the time of this interim analysis, the observed difference in median overall survival favored TCF over CF (9.2 vs 8.6 months, respectively; $P = 0.0201$). The common severe toxicities associated with TCF and CF included stomatitis (20.8% and 27.2% of subjects, respectively), lethargy (21.3% and 17.9%), diarrhea (20.4% and 8.0%), nausea (15.8% and 18.8%), vomiting (14.9% and 18.8%), and febrile neutropenia or neutropenic infection (30% and 13.5%). Based on the results of the TAX325 trial, TCF is regarded as standard chemotherapy in the United States.

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Until the early 1990s there was no standard chemotherapy in Japan, although 5-FU infusion, CF, and uracil-tegafur, and mitomycin C (UFTM) regimens were widely employed in the clinical setting. In a three-arm, large randomized phase III trial, Ohtsu et al.[12] compared 5-FU with CF and with UFTM. They found 5-FU to be equal to or better than UFTM in terms of response and survival. Although CF achieved a better response rate and progression-free survival (PFS) than 5-FU monotherapy, there was no difference in overall survival between these two arms (7.3 and 7.1 months for CF and 5-FU, respectively). 5-FU monotherapy remained as a reference arm in the next phase III trial of the JCOG group.

New Anticancer Agents

S-1 consists of a 1:0.4:1 molar ratio mixture of tegafur and two 5-FU-modulating substances: gimeracil (5-chloro-2,4-dihydroxypyrimidine, CDHP) and oteracil (potassium oxonate). Sakata et al.[13] investigated the efficacy of S-1 as a single chemotherapeutic agent in AGC patients in a late phase II study. Four cycles of S-1 were administered twice a day to 51 patients at a dose of 80 mg/m^2 per day. One complete response (CR) and 24 partial responses (PRs) were observed, with an overall response rate of 49%. The median survival time (MST) achieved by S-1 in a phase II study was 8 months and it was generally well tolerated, the major toxicities including anemia, leukopenia, granulocytopenia, diarrhea, malaise, and proteinuria.

Boku et al.[14] reported a phase II trial of cisplatin/CPT-11 combination chemotherapy involving 44 patients with AGC by the JCOG. Cisplatin was administered at a dose of 80 mg/m^2 on day 1, and CPT-11 was administered at a dose of 70 mg/m^2 on days 1 and 15 every 4 weeks. They reported 1 CR and 20 PR, with an overall response rate of 48.0%, and an MST of 9 months. The grade 4 major toxicities with this combination were leukopenia (9.0%), neutropenia (57.0%), thrombocytopenia (2.0%), and anemia (5.0%).

JCOG 9912 Trial

The JCOG conducted another three-arm, randomized phase III trial in 1999 (the JCOG 9912 trial), evaluating the superiority of cisplatin/CPT-11 over the reference arm 5-FU, and the noninferiority of S-1 to 5-FU. The MSTs achieved by 5-FU, cisplatin/CPT-11, and S-1 were 10.8 months, 12.3 months, and 11.4 months,

respectively. Survival was not significantly better with cisplatin/CPT-11 vs 5-FU ($P = 0.055$); however, the non-inferiority of S-1 vs 5-FU was confirmed ($P < 0.001$). Subsequently, S-1 has been widely used in Japan as the standard and first-line chemotherapy for AGC.

Combination Chemotherapy with S-1

The efficacy of combination chemotherapy with S-1 in AGC has been assessed in a number of phase I/II studies. Cisplatin at a dose of 60 mg/m^2 on day 8 was combined with S-1 for 3-weeks-on and 2-weeks-off.[15] Treatment was repeated every 5 weeks, unless disease progression was observed. The subjects of this trial were 19 AGC patients, and the incidences of severe (grade 3/4) hematological and nonhematological toxicities were 15.8% and 26.3%, respectively, but all cases were manageable. The response rate was 74% (14/19; 95% confidence interval, 54.9–90.6), and the MST was 383 days.

Komatsu et al.[16] reported the results of a phase I/II study with CPT-11 and S-1 (IRIS) in AGC patients. S-1 was given orally twice a day for 14 days, and CPT-11 was administered as a 90-min intravenous infusion on days 1 and 15. This regimen was repeated every 4 weeks. Fifteen patients were registered in the phase I study and 9 were added to the phase II study. Most of the nonhematological toxicities were classified as grade 2 or lower, except for grade 3 nausea and grade 3 level 2 dermatitis. The hematological toxicities consisted of grade 4 neutropenia in one patient at level 1 and level 2 in phase I, and grade 4 neutropenia in 4 patients at level 2 in phase II. All of these patients recovered after the drug was suspended. These side effects were tolerable, and the overall response rate was 54.2%. The MST achieved with this regimen was 581 days.

Yoshida et al.[17] performed a phase I study and a phase II study of docetaxel in combination with S-1 in patients with AGC. In the phase I study, neutropenia and leukocytopenia were the dose-limiting toxicities (DLTs). The recommended dose (RD) was 40 mg/m^2 on day 1 for docetaxel and 80 mg/m^2 on days 1–14 for S-1, every 3 weeks. In the phase II study, the response rate was 52.1% and the MST was 434 days. The most common severe toxicities were neutropenia (18.5%), leukopenia (12.3%), anemia (2.6%), stomatitis (10.4%), anorexia (6.3%), and nausea (6.3%). Yamaguchi et al.[18] reported a phase I/II study of docetaxel in combination with S-1. During dose escalation, G3 infection without neutropenia was the DLT. The RD was 40 mg/m^2 on day 1 for docetaxel and 80 mg/m^2 on days 1–14 for S-1, every 4 weeks. The response rate was 45.7%, the MST was 14.2 months, and the PFS was 4.3 months. The most common severe toxicities were neutropenia (67.4%), leukopenia (41.3%), anemia (21.7%), anorexia (21.7%), nausea (6.5%), and stomatitis (6.5%).

Phase III Trials of S-1 Monotherapy vs S-1 in Combination

Based on the results obtained in the above phase II studies, three large randomized phase III studies, the SPIRITS trial, the TOP-002 trial, and the JACCRO GC03 trial, were conducted independently to compare data with that of S-1 monotherapy. In the SPIRITS trial,[19] chemotherapy-naïve patients with AGC were randomly assigned to receive either S-1 plus cisplatin or S-1 alone. In the patients assigned to receive S-1 plus cisplatin, the S-1 (40–60 mg depending on the patient's body surface area) was given orally, twice daily for 3 consecutive weeks, and 60 mg/m^2 cisplatin was given intravenously on day 8, followed by a 2-week rest period within a 5-week cycle. Patients assigned to receive S-1 alone were given the same dose of S-1 twice daily for 4 consecutive weeks, followed by a 2-week rest period, within a 6-week cycle. The primary endpoint was overall survival and the secondary endpoints were PFS, proportion of responders, and safety. Of the 305 patients enrolled, 7 were ineligible or withdrew consent, 148 patients were assigned to the S-1 plus cisplatin group, and 150 were assigned to the S-1 alone group. Median overall survival was significantly longer in the patients assigned to receive S-1 plus cisplatin than in those assigned to receive S-1 alone (13.0 vs 11.0 months, respectively; hazard ratio, 0.77; 95% confidence interval, 0.61–0.98; $P = 0.04$). The PFS was significantly longer in the patients assigned to receive S-1 plus cisplatin than in those assigned to receive S-1 alone (median PFS, 6.0 months vs 4.0 months, respectively; $P < 0.0001$). Moreover, of the 87 patients with target tumors, assigned to receive S-1 plus cisplatin, 1 showed a CR and 46 showed a PR (total response rate, 54%), and of the 106 patients with target tumors, assigned to receive S-1 alone, 1 showed a CR and 32 showed a PR (total response rate, 31%). Grade 3 or 4 adverse events including leukopenia, neutropenia, anemia, nausea, and anorexia were reported in the group assigned to S-1 plus cisplatin rather than in the group assigned to S-1 alone. There were no treatment-related deaths in either group. Based on this trial, S-1 plus cisplatin became regarded as a new standard first-line treatment for patients with AGC in Japan.

A randomized phase III trial was conducted to evaluate the efficacy and safety of IRIS (S-1/CPT-11) vs S-1 for AGC.[20] Patients with previously untreated AGC were randomized to Arm A (oral S-1, 80 mg/m^2 on days 1–28, every 6 weeks) or Arm B (IRIS: oral S-1,

80 mg/m^2 on days 1–21; and intravenous irinotecan, 80 mg/m^2 on days 1 and 15, every 5 weeks) by dynamic allocation. Treatment was continued unless disease progression or unacceptable toxicity was observed. The primary endpoint was overall survival and the secondary endpoints were 1-year survival, response rate, and toxicity. As a result, 326 patients were randomized to Arm A (162 patients) or Arm B (164 patients), with a final 315 evaluable patients (160 in Arm A and 155 in Arm B). The patients' characteristics were well balanced in the two groups. By the end of the trial, 247 events (78%) had been observed. Although the MST of the Arm A patients was 318 days (95% confidence interval, 286–395) and that of the Arm B patients was 389 days (95% confidence interval, 324–458), Arm B did not show significant superiority to Arm A (log-rank test P = 0.23; hazard ratio = 0.86). The 1-year survival rates were 44.9% in Arm A and 52.0% in Arm B. The response rates were significantly different, being 26.9% in Arm A vs 41.5% in Arm B (chi-square test; P = 0.035) in 187 RECIST (Response Evaluation Criteria In Solid Tumors) evaluable patients. The most common grade 3/4 toxicities in Arm A vs Arm B were neutropenia (10.6% vs 27.1%), diarrhea (5.6% vs 16.1%), anorexia (18.8% vs 17.4%), nausea (5.6% vs 7.1%), and vomiting (1.9% vs 3.2%). Based on this trial, IRIS achieved MST and was better tolerated; however, IRIS did not show significant superiority to S-1 alone in terms of the overall survival. Thus, IRIS could not become a first-line treatment for AGC.

A randomized phase III study comparing S-1 alone with the S-1/docetaxel combination is ongoing through the JACCRO GC03 trial.[21] This study is a prospective, multicenter, multinational (Korea and Japan), nonblinded, randomized, phase III study of patients with AGC. Patients are randomly assigned to receive 3-week cycles of Treatment Arm A (docetaxel and S-1) or 6-week cycles of Treatment Arm B (S-1 only). The primary objective of the study is to compare the median overall survival of the test arm (docetaxel and S-1) with that of the control arm (S-1 only) in patients with AGC. The secondary objectives are to assess the time to tumor progression (TTP), defined as the time from randomization to the date of first documentation of progressive disease (PD); to determine the clinical response (RR = response rate), defined as the sum of the CR and PR according to the RECIST; and to evaluate the safety of the two regimens. It was expected that 628 patients (314 in each treatment arm) would be enrolled in this trial and this has been exceeded, with 628 patients from 103 centers confirmed in September 2008. The first author of this review is a principal participating investigator in this trial, the results of which will be available in 2010.

Future Perspectives of Standard Chemotherapy

If the results of the S-1/docetaxel combination are positive, both S-1/docetaxel and S-1/cisplatin will offer standard care options for AGC. A triplet of the S-1/cisplatin/docetaxel combination is expected as the next candidate of the standard regimen.[22] The replacement of heavy metals from cisplatin to oxaliplatin in the combination with S-1 is also expected. Some molecular target agents have already been investigated for AGC. These agents of the new generation are expected to make revolutionary progress in chemotherapy for unresectable or recurrent GCs.

Second-Line Chemotherapy

Weekly paclitaxel or cisplatin/CPT-11 is widely used as second-line chemotherapy, but there is no established regimen for patients with AGC failing to respond to, or with progression after, first-line chemotherapy. Although there are some phase III studies ongoing, the treatment of S-1 refractory GC remains controversial with regard to whether S-1 should be continued as a second-line. After the successful adjuvant S-1 results (ACTS-GC trial),[23] the same problem will arise in patients receiving adjuvant S-1 for recurrence. The JACCRO GC05 trial is a randomized phase II/III trial of second-line chemotherapy comparing CPT-11 monotherapy with the S-1/CPT-11 combination for S-1 refractory GC. We expect that the results of this study will resolve the controversy.

Neoadjuvant Chemotherapy (NAC)

Japanese surgeons can control N2 lymph node metastasis by standard gastrectomy with D2 dissection. Neoadjuvant chemotherapy for high-risk patients with AGC is important to increase the chance of curative resection and make unresectable GC tumors resectable by downstaging the tumor. Tumors with H0, P0, T3, T4, or N3 are most suitable for this therapy. The downstaging of lymph node metastasis of N3 or over to controllable N2 is the main target of NAC. Other distant metastasis, such as hepatic, lung, or peritoneal dissemination, is usually treated by chemotherapy first, and is not a target of NAC. S-1/cisplatin is widely used for the NAC regimen based on the high response rate reported in a phase II trial.[15] Randomized controlled phase III studies are needed in conjunction with accurate staging of the disease by laparoscopy. The results of histopathologic examination of resected materials following preoperative chemotherapy are thought to be an indicator of chemosensitivity in the postoperative adjuvant setting.

As yet, there is no clear evidence of the utility of NAC for GC, but its benefits will be proved soon by randomized controlled trials.

Adjuvant Chemotherapy

Before 2004, no positive results of adjuvant chemotherapy for curatively resected GC were reported. In the United States, the INT-0116 showed that adjuvant chemoradiation prolonged survival and relapse-free survival.[24] However, most of the patients in this study underwent D0 or D1 surgery, whereas only 10% underwent D2 lymphadenectomy. The European MAGIC trial, performed mainly in the United Kingdom, showed that perioperative and postoperative chemotherapy with ECF significantly prolonged overall survival and progression-free survival. In that study, D2 surgery was not the standard procedure, as it is in Japan. Comparisons of adjuvant chemotherapy vs surgery alone after D2 surgery in Japan were not positive.

In 2007, Nakajima et al.[25] reported positive results of adjuvant UFT based on the NSAS GC trial. In this trial, patients with TNM (tumor node metastasis) stage T2 N1-2 GC were randomly assigned to undergo surgery alone or to undergo surgery followed by postoperative UFT 360 mg/m^2 per day orally for 16 months. However, this trial was terminated before the target number of patients had been reached as accrual was slower than expected, with 190 patients registered and 95 randomized to each group. Nevertheless, after a median follow-up of 6.2 years, the overall and relapse-free survival rates were significantly higher in the surgery+chemotherapy group (hazard ratio for overall survival 0.48, $P = 0.017$; hazard ratio for relapse-free survival 0.44, $P = 0.005$). Furthermore, in 2007 Sakuramoto et al.[23] reported the success of adjuvant S-1 chemotherapy in patients with curatively resected GC. Patients with stage II or III GC who underwent gastrectomy with D2 dissection were randomly assigned to undergo surgery followed by adjuvant therapy with S-1 or to undergo surgery only. In the surgery+S-1 group, S-1 was started within 6 weeks after surgery and continued for 1 year. The treatment regimen consisted of 6-week cycles in which, in principle, 80 mg/m^2 of oral S-1 per day was given for 4 weeks and no chemotherapy was given for the following 2 weeks. There were 529 patients assigned to the surgery+S-1 group and 530 patients assigned to the surgery-only group between October 2001 and December 2004. The trial was stopped on the recommendation of independent data and the safety monitoring committee, because the first interim analysis, performed 1 year after enrollment was completed, showed that the surgery+S-1 group had a higher overall survival rate than the surgery-only group ($P = 0.002$). Analysis of follow-up data showed that the 3-year overall survival rate was 80.1% in the surgery+S-1 group and 70.1% in the surgery-only group. The hazard ratio for death in the surgery+S-1 group vs the surgery-only group was 0.68 (95% confidence interval, 0.52–0.87; $P = 0.003$). Adverse events of grade 3 or grade 4 (defined according to the Common Toxicity Criteria of the National Cancer Institute), which were relatively common in the surgery+S-1 group, were anorexia (6.0%), nausea (3.7%), and diarrhea (3.1%). It was concluded that S-1 is an effective adjuvant treatment for patients who have undergone a D2 dissection for locally advanced GC.

Conclusions

1. The standard regimen now used for AGC in Japan is the S-1/cisplatin combination, and we are awaiting the trial results about S-1/docetaxel combination chemotherapy. If the results of this S-1/docetaxel combination are positive, both S-1/docetaxel and S-1/cisplatin will offer standard care options for AGC.
2. Weekly paclitaxel or cisplatin/CPT-11 is widely used as second-line chemotherapy after refractory S-1, but there is still no standard second-line regimen until ongoing phase III results are reported.
3. Neoadjuvant chemotherapy for high-risk patients with AGC is important to increase the chance of curative resection and make unresectable GC tumors resectable by downstaging the tumor. Downstaging of N3 (or more) lymph node metastasis to controllable N2 is the main target of NAC.
4. The standard chemotherapy for T2 N1-2 GC after D2 dissection is adjuvant UFT, and that for stage II, III GC after D2 dissection is adjuvant S-1.

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ORIGINAL ARTICLE

An analysis of risk factors for pancreatic fistula after pancreaticoduodenectomy: clinical impact of bile juice infection on day 1

Takahiro Kajiwara · Yoshihiro Sakamoto · Noriaki Morofuji · Satoshi Nara · Minoru Esaki · Kazuaki Shimada · Tomoo Kosuge

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Abstract
Background Postoperative pancreatic fistula (POPF) is a most striking complication after pancreatic resection. The objective of this study is to reveal the risk factors for POPF defined by the international study group after pancreaticoduodenectomy in a Japanese high-volume center.
Methods During the recent 4 years, 220 patients underwent pancreaticoduodenectomies. In patients of obstructive jaundice, preoperative biliary drainage was performed by percutaneous (n=71) and/or retrograde (n=38) approach. Pancreaticojejunostomy was performed using either duct-to-mucosa anastomosis (n=180) or dunking method (n=40). Risk factors for POPF (grade B or grade C POPF by international definition) were evaluated using univariate and multivariate analyses.
Results POPF was found in 109 (50%) patients; grade A in 45 (21%), grade B in 54 (25%), and grade C in 10 patients (5%). One patient died of intra-abdominal hemorrhage caused by POPF. Univariate and multivariate analyses revealed that independent risk factors for grade B or grade C POPF were the size of the main pancreatic duct (<3 mm; relative risk (RR), 3.3; p=0.002), body mass index (≥20, RR 2.5, p=0.03), and bile juice infection on day 1 (RR, 2.2; p=0.04). The performance of biliary drainage or method of pancreaticojejunostomy was not a significant risk factor for POPF. Bile juice infection on day 1 was significantly associated with retrograde biliary drainage (p<0.001).
Conclusions Bile juice infection on day 1 was a significant risk factor for grade B or grade C POPF after pancreaticoduodenectomy. Although the performance or the status of biliary drainage itself was not a risk factor for POPF, percutaneous biliary drainage might be advantageous against retrograde drainage to reduce the risk of biliary infection.

Keywords Pancreaticoduodenectomy · Postoperative pancreatic fistula (POPF) · Biliary drainage · Bile juice infection

T. Kajiwara · Y. Sakamoto (✉) · N. Morofuji · S. Nara · M. Esaki · K. Shimada · T. Kosuge
Hepatobiliary and Pancreatic Surgery Division,
National Cancer Center Hospital,
5-1-1Tsukiji, Chuo-ku,
Tokyo 104-0045, Japan
e-mail: yosakamo@ncc.go.jp

Introduction

With the advancement of imaging studies, surgical techniques, and perioperative management, the mortality rate of pancreaticoduodenectomy has decreased to 0–9% in high-volume centers. However, the morbidity rate still remains in the range of 30–50% [1–3], and postoperative pancreatic fistula (POPF) is the most common complication of pancreaticoduodenectomy, which would lead to not only prolongation of the hospital stay but also lethal morbidity or surgical mortality. The incidence of POPF is reported to be 0–17% base on a variety of definition of pancreatic fistula [4–6]. Recently, an international study group of pancreatic fistula (ISGPF) defined POPF by reviewing numerous reported series [7]. ISGPF classified POPF into three categories, grade A as a transient or minor fistula, grade B as a major fistula with prolongation of hospital stay, and grade C necessitating surgical intervention. This classification is useful to evaluate the incidence of POPF objectively throughout the age and institution [8]. In the present study, we focused on grade B

and grade C POPF after pancreaticoduodenectomy and analyzed the risk factors for POPF in a Japanese high-volume center hospital.

Patients and methods

Between August 2003 and December 2006, 220 patients underwent pancreaticoduodenectomies in our institute. The diseases included invasive pancreatic cancer in 108 patients, bile duct cancer in 26 patients, ampullary or duodenal cancer in 33 patients, intraductal papillary mucinous tumor in 22 patients, neuroendocrine tumor in 9 patients, gallbladder cancer in 2 patients, metastatic cancers in 2 patients, and other diseases in 18 patients. Five staff surgeons performed all of the operations. One chief resident and one resident assisted each attending surgeon perioperatively.

Surgical procedures of pancreaticoduodenectomy

The details of our standard surgical procedure of pancreaticoduodenectomy have been described elsewhere [9]. All of the patients with obstructive jaundice (n=101) underwent only percutaneous biliary drainage (PTCD, n=63), only endoscopic retrograde biliary drainage (n=30) or both of PTCD and retrograde biliary drainage (n=8) in the previous hospital or in our institute. The remaining 119 patients underwent pancreaticoduodenectomy without biliary drainage. Pancreaticoduodenectomy was performed when the serum bilirubin concentration decreased less than 5 mg/dl. Patients received preoperative intravenous antibiotic prophylaxis using a second-generation cephalosporin. After removal of the pancreatic head, we routinely wrapped the stump of the gastroduodenal artery using the falciform ligament to prevent the bleeding caused by pancreatic leakage [10]. The surgical procedures consisted of standard Whipple procedure (SW) in 58 patients and pylorus-preserving pancreaticoduodenectomy (PPPD) in 162 patients. Combined portal vein resection was performed in 54 patients (24.5%) of all 220 patients; 48 patients with pancreatic invasive cancer, 3 patients with bile duct cancer, and 3 patients with other disease.

Pancreaticojejunostomy was performed in 217 out of 220 patients. In the remaining three patients, the remaining pancreatic parenchyma was left unreconstructed or external pancreatic tube was placed because the remaining pancreatic parenchyma was very small. A jejunal loop was lifted, and pancreaticojejunostomy was performed by duct-to-mucosa anastomosis (n=180) or dunking method (n=40) with external drainage (n=215), or with internal stent (n=5). The anterior and posterior pancreatic walls were tightly affixed to the jejunal serosa by interrupted sutures. Hepaticojejunostomy was then made by interrupted sutures with external drainage (n=209), with internal stent (n=7), or without stenting (n=4).

An antecolic gastrojejunostomy and duodenojejunostomy were performed in SW and PPPD, respectively. The anastomosis was made by the Albert-Lembert (n=200), layer-to-layer (n=7), Gambee method (n=2), or stapled mechanical anastomosis (n=11). A Braun jejunojejunostomy was made to prevent direct exposure of the anastomotic site to pancreatic and bile juice (n=127). Gastric tubes and jejunal feeding tubes were placed in 126 and 148 patients, respectively. In 11 patients, stapled Roux-en-Y reconstruction was performed using ILS (Proximate ILS™ 29 or 25 mm, Ethicon Endo-Surgery, Cincinnati, OH, USA) in PPPD (n=6) or ENDO-GIA (ENDO-GIA Roticulator™ 60, US Surgical, Norwalk, CT, USA) in SW (n=5) [11].

Two closed drains, sized 8 or 10 mm in diameter, were inserted beside the pancreatojejunostomy, and intermittent suction of the drainage fluid was performed in principle. When amylase-rich fluid was discharged from the drain on postoperative day 4–7, the drains were cut to let out the infectious fluid. Most of the patients underwent external drainage of bile juice via hepaticojejunostomy, and we routinely cultured bacteria in the bile juice on day 1. Drains were exchanged under fluoroscope on day 14; thereafter, they were exchanged as required until removal. Patients were allowed to be discharged from the hospital and to go home, when they could eat almost half of the regular diet and had one abdominal drain left with slight output.

Definition of outcome measures

POPF was defined according to the definition proposed by an international study group on pancreatic fistula [7], i.e., when the amylase concentration of the drain fluid obtained on or after postoperative day 3 was greater than three times the serum amylase concentration. Pancreatic fistulas were classified into grades A, B, and C according to severity; briefly, grade A was "transient fistula", not associated with a delay in hospital discharge; grade B fistula led to a delay in discharge, with persistent drainage for more than 3 weeks; and a grade C fistula was usually associated with major complications. Because grade A POPF can be a "transient" fistula, we focused on the risk factors for grade B and grade C POPF, which are significant POPF associated with prolongation of hospital stay.

Delayed gastric emptying (DGE) were classified into grades A, B, and C according to the recent report [12], i.e., in grade A, patient was unable to tolerate solid oral intake by seven postoperative days, and vomiting is uncommon; whereas in grades B and C, there is usually vomiting. In grade B, patient was unable to tolerate solid oral intake by

14 postoperative days; in grade C, 21 postoperative days. Grades B and C DGE were considered to be significant complications.

Univariate and multivariate analysis of risk factors for POPF

Univariate analyses of risk factors for POPF (grade B or C) were performed in relation to the following clinicopathological variables, including age (≥65, <65), sex, body mass index (BMI, ≥20, <20), carcinoembryonic antigen (≥5, <5 ng/mL), CA19-9 (≥37, <37 IU/mL), the disease, dilatation of the main pancreatic duct (≥3, <3 mm), status of preoperative biliary drainage, duration of operation (≥540, <540 min), operative blood loss (≥800, <800 mL), surgical procedures (PPPD vs SW), method of pancreaticojejunostomy (duct-to-mucosa anastomosis or dunking method), placement of external pancreatic drainage, duration of hospital stay (days), and bile juice infection on day 1. The thresholds of age, BMI, duration of operation, and operative blood loss were determined on the median value of each parameter. Multivariate analyses were conducted using the significant factors in the univariate analyses.

Statistical analysis

Analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Windows statistical software (SPSS Inc., Chicago, IL, USA). Chi-square test or Fisher's exact test for univariate analysis and Mann–Whitney *U* test were used to compare the variables between the two groups. Data were expressed as median and range. A p value of less than 0.05 was considered statistically significant.

Results

The overall mortality rate was 0.9% (n=2). One patient developed massive intra-abdominal bleeding on day 7 and died of hypovolemic condition. Another patient was found to have Guillain–Barre syndrome on day 10 and died of respiratory failure. Postoperative surgical complication included POPF in 109 patients (50%), grade A in 45 (20%), grade B in 54 (25%), and grade C in 10 (5%); grade B or grade C DGE in 61 patients (28%), wound infection in 18 patients (8%), intra-abdominal collection in 18 patients (8%), bile leakage in 2 patients (0.9%), gastric leakage in 2 patients (0.9%), liver abscess in 3 patients (1.3%), pulmonary embolism in 3 patients (1.3%), hemorrhage in 4 patients (1.8%), and others in 12 patients (5.5%). Seven patients (3.2%) required reoperation.

Univariate and multivariate analysis of risk factors for grade B and grade C POPF

In the univariate analysis, seven variables, gender (male), gender (≥65), BMI (≥20), disease (other than pancreatic cancer), the size of the main pancreatic duct (<3 mm), portal vein resection (not performed), and bile juice infection on day 1, were identified as significant risk factors for grade B and grade C POPF (Table 1). No statistical difference was found in the incidence of grade B or grade C POPF between patients undergoing only PTCD (n=63) and patients undergoing only retrograde drainage (n=30; 25% vs 27%, p=0.73). The performance or status of biliary drainage and the method of pancreaticojejunostomy were not significant risk factors for POPF. Multivariate analysis revealed that size of the main pancreatic duct (<3 mm), BMI (≥20), and bile juice infection on day 1 were independent risk factors for grade B and grade C POPF (Table 2).

Status of the biliary drainage and the results of the culture of the bile juice infection on day 1 after pancreaticoduodenectomy

Relationship between the status of biliary drainage and bile juice infection on day 1 after pancreaticoduodenectomy are listed in Table 3. Positive culture of the bile juice on day 1 was found in 17 out of 97 patients (18%) without biliary drainage, 19 out of 48 patients (40%) undergoing only PTCD, and 19 out of 26 patients (65%) undergoing only retrograde biliary drainage. There was a significant relationship between the status of the biliary drainage and the culture of bile juice on day 1 after pancreaticoduodenectomy (p<0.001). The incidence of bile juice infection was significantly higher in patients with biliary drainage than that in patients without biliary drainage (52% vs 18%, p<0.001) and was significantly higher in patients with retrograde drainage than that in patients with only percutaneous drainage (40% vs 65%, p=0.006).

Results of the culture of the bile juice on day 1 are listed in Table 4. *Enterococcus* and *Enterobacter* are the leading bacteria in the bile juice on day 1.

Discussion

In the present study, we evaluated the risk factors for grade B and grade C POPF after pancreaticoduodenectomy based on the recent definition by the international study group in a Japanese high-volume center. As a result, size of the main pancreatic duct (<3 mm), BMI (≥20), and bile juice infection on day 1 were independent risk factors for grade B and grade C POPF. Among the three risk factors, the former two variables would be associated with the

Table 1 Univariate analysis of risk factors for postoperative pancreatic fistula (grade B and grade C) after pancreaticoduodenectomy

Variables		No pancreatic fistula or POPF, grade A (n=156)	POPF, grade B or C (n=64)	p value
Patient characteristics				
Gender	Male	80	45	0.010*
	Female	76	19	
Age, years	≥65	69	43	0.002*
	<65	87	21	
Mean BMI	≥20	71	46	<0.001*
	<20	85	18	
Disease	Pancreatic cancer	91	17	<0.001*
	Other disease	65	47	
MPD dilatation	≥3 mm	110	19	<0.001*
	<3 mm	46	45	
Status of biliary drainage				
Preoperative biliary drainage	Performed	71	30	0.85
	Not performed	85	34	
Retrograde biliary drainage	Not performed	129	53	0.98
	Performed	27	11	
Percutaneous biliary drainage	Not performed	107	42	0.67
	Performed	49	22	
Surgical procedures				
Procedure of PD	SW	42	16	0.80
	PPPD	113	47	
Pancreaticojejunostomy	Duct-to-mucosa anastomosis	128	52	0.89
	Dunking method	28	12	
Length of operation, min	>9 h	77	25	0.16
	<9 h	79	39	
Blood loss, mL	≥800 ml	76	35	0.42
	<800 ml	80	29	
Portal vein resection	Not performed	47	7	0.003*
	Performed	109	56	
Postoperative information				
Culture of bile juice on day 1	Negative	93	26	<0.001*
	Positive	31	28	
	Not determined	32	10	
Mortality		0 (0%)	2 (3.1%)	0.03
Duration of hospital stay (days)		24 (9–83)	39 (21–324)	<0.001*

POPF postoperative pancreatic fistula, *BMI* body mass index, *MPD* main pancreatic duct, *SW* standard Whipple procedure, *PPPD* pylorus-preserving pancreaticoduodenectomy

*p<0.05

characteristics of the patients and the disease. On the other hand, bile juice infection on day 1 practically signifies the bile juice has already contaminated preoperatively. Bile juice contamination would be largely brought by preoperative biliary drainage. Actually, bile juice infection on day 1 was found in 18% of patients without biliary drainage, 40% of patients undergoing only PTCD, and 65% of patients undergoing retrograde biliary drainage. Although the performance of biliary drainage itself was not a significant risk factor for POPF, the above results may suggest that (1)

Table 2 Multivariate logistic regression of risk factors for postoperative pancreatic fistula (grade B and grade C) after pancreaticoduodenectomy

Factors	Odds ratio	95% confidence interval	p value
Size of the main pancreatic duct <3 mm	3.284	1.538–7.014	0.002
BMI ≥20	2.428	1.094–5.387	0.03
Bile juice infection on day 1	2.235	1.033–4.836	0.04

Table 3 Status of the biliary drainage and culture of bile juice infection on day 1 after pancreaticoduodenectomy

	Culture of bile juice on day 1		*p* value
	Negative (n=119)	Positive (n=59)	
No biliary drainage	80 (82%)	17 (18%)	<0.001
PTCD alone	29 (60%)	19 (40%)	
Retrograde drainage alone	7 (35%)	19 (65%)	
Both PTCD and retrograde drainage	3 (43%)	4 (57%)	

PTCD percutaneous transhepatic biliary drainage

preoperative biliary drainage will evoke the biliary infection, and (2) when biliary drainage is necessary, PTCD might be advantageous against retrograde drainage in the viewpoint of reducing biliary infection.

In this study, the definition of POPF was determined by the international definition recently proposed by the international study group of pancreatic surgery [7]. The incidence of POPF (48%) in our institute was much higher than the reported series [1–8]. However, we routinely measured the amylase concentration in the drainage fluid, and we carefully did not remove the drains until the amylase-rich or infected fluid goes out. Our relatively conservative management might further prolong the drain placement and increase the chance of second infection [13]. In some reports [3, 14], the incidence of POPF was very low, while the incidence of intra-abdominal hemorrhage and/or the mortality rate are high. In these studies, some patients with occult POPF [6] might be discharged, and they might be back to the hospital with intra-abdominal abscess or hemorrhage, which can lead to life-threatening events.

Bile juice infection on day 1 was associated with POPF and also with the performance or method of biliary drainage. Some randomized trials have revealed that preoperative biliary drainage increased surgical morbidity, including wound infection and POPF [15, 16], which could explain that biliary infection caused by biliary drainage would increase infections complication. Povoski et al. reported that intra-abdominal infection, morbidity, and mortality were more often in patients with preoperative biliary drainage [15]. Because occult POPF can sometimes present with intra-abdominal abscess, we suppose that biliary infection, caused by biliary drainage, can increase the incidence of intra-abdominal infection and also the incidence of POPF. Others have reported that preoperative biliary drainage did not increase the surgical risks after pancreaticoduodenectomy [17–19]. Some randomized trial has denied the clinical significance of preoperative biliary drainage before pancreaticoduodenectomy, but most of the enrolled patients underwent palliative surgery, and any randomized trial considering for patients undergoing pancreaticoduodenectomy has never been conducted. In most reports, preoperative biliary drainage did not decrease surgical complications, and they concluded that it should be avoided if possible. Nevertheless, 50–70% of patients underwent pancreatic resection after preoperative biliary drainage [15–19]. This is partly because patients were referred to a high-volume center following biliary drainage in primary care centers. As persistent obstructive jaundice will provoke general fatigue, itching, and hepatobiliary dysfunction, biliary drainage will be absolutely necessary in some patients to improve the general condition.

Table 4 Results of culture of the bile juice on day 1 after pancreaticoduodenectomy

Positive/negative	*n*	Bacteria	*n*
Positive	59	*Enterococcus*	24
		Enterobacter	22
		Klebsiella	8
		Pseudomonas	6
		Streptococcus	4
		Citrobacter	4
		Aeromonas	3
		Staphylococcus	2
		Bacteroides	2
		Stenotrophomonas	2
		Other six bacteria	1
Negative	119		
Not determined	42		

In our study, the incidence of bile infection was higher in patients undergoing retrograde drainage than in patients undergoing percutaneous drainage. However, superiority of percutaneous or retrograde drainage prior to pancreaticoduodenectomy has not been elucidated by any randomized trials [20]. This issue should be further investigated by a prospective study.

In the multivariate analysis, BMI and the size of the main pancreatic duct were other risk factors for POPF. It has been repeatedly described that normal, soft pancreas with thin main pancreatic duct is closely associated with POPF [2, 3]. The incidence of POPF of patients with duct-to-mucosa anastomosis was similar with that of patients with dunking method (29% vs 30%, p=0.89). Although duct-to-mucosa anastomosis has been willingly introduced in order to reduce the incidence of POPF [5], no well-designed randomized trial has revealed the efficacy of duct-