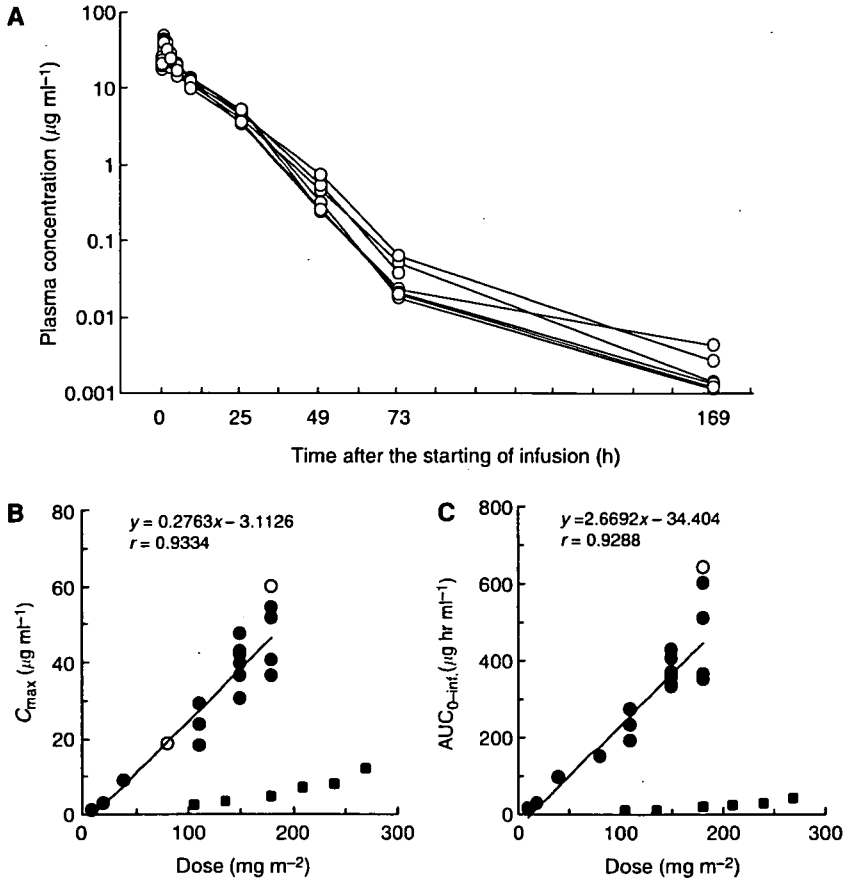

Figure 2 (**A**) Individual plasma concentrations of PTX in seven patients following 1-h intravenous infusion of NK105 at a dose of 150 mg m^{-2}. (**B**) Relationships between dose and C_{max}, and (**C**) between dose and $AUC_{0-inf.}$ of PTX in patients following 1-h intravenous infusion of NK105. Regression analysis for dose *vs* C_{max} was applied using all points except one patient at 80 mg m^{-2} whose medication time became 11 min longer and one patient at 180 mg m^{-2} who had medication discontinuation and steroid medication. (Plots were shown as open circle). Regression analysis for dose *vs* $AUC_{0-inf.}$ was applied using all points except one patient who had medication discontinuation and steroid medication. (Plot was shown as open circle.) Relationships between dose and C_{max}, and $AUC_{0-inf.}$ in patients following conventional PTX administration were plotted (closed square, see Tamura *et al*, 1995).

Table 3 Pharmacokinetic parameters

	Dose (mg m^{-2})	*n*	C_{max} (μg ml^{-1})	$AUC_{0-inf.}$ (μg h ml^{-1})	$t_{1/2}$ (h)	CL_{tot} (ml h^{-1} m^{-2})	V_{ss} (ml m^{-2})	UE[a] (%)	CL_r (ml h m^{-2})
NK105	10	1	0.9797	11.4	9	880.4	10400.3	7.5	66.4
	20	1	2.8971	29.1	8.5	687.9	8027	8.6	59.4
	40	1	8.8334	93.9	13.2	426.1	5389.8	5.2	22
	80	1	18.4533	149.3	7	535.8	5875.8	4.7	25.3
	110	3	23.3924	232	9.7	483.3	5881.2	7.6	35.6
			±5.6325	±39.1	±1.6	±82.7	±1512.0	±1.7	±6.9
	150	7	40.1699	369.8	10.6	408.6	4527.1	5.3	21.6
			±5.5334	±35.2	±1.3	±37.3	±639.5	±1.5	±6.5
	180	4[b]	45.6278	454.5	11.3	416.5	4983.4	5.9	23.7
			±8.6430	±119.1	±0.6	±104.7	±887.5	±1.4	±4.2

[a]UE, urinary excretion. [b]One patient at 180 mg m^{-2} level was omitted from the calculation of summary pharmacokinetic parameters, as there was administrating interruption for developing allergic reactions.

Indeed, the results of this clinical trial show that NK105 can be administered safely as a short infusion (1 h) without the administration of antiallergic agents like dexamethasone and antihistamine, although one patient at 180 mg m^{-2} developed transient grade 2 hypersensitivity at the first course. Therefore, NK105 may offer advantages in terms of safety and patient convenience and comfort.

The pharmacokinetic analysis of NK105 suggests that the distribution of PTX-incorporating micelles is mostly restricted to the plasma and, in part, to extracellular fluids in the body. This is consistent with data obtained in a preclinical study (Hamaguchi *et al*, 2005) showing that the distribution of NK105 in tissues is characterised by an EPR effect, similar to that of tumour and inflammatory lesions, or by the presence of a reticuloendothelial

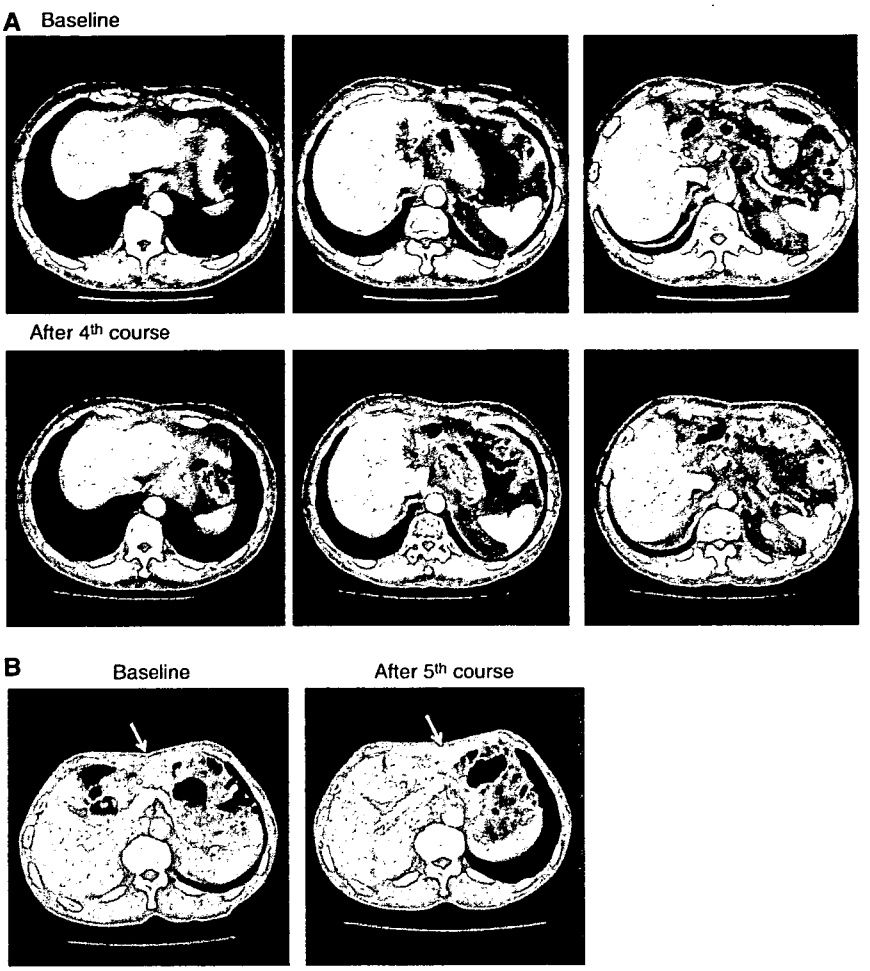

Figure 3 Serial CT scans. (**A**) A 60-year-old male with pancreatic cancer who was treated with NK105 at a dose level of 150 mg m^{-2}. Baseline scan (upper panels) showing multiple metastasis in the liver. Partial response, characterized by a more than 90% decrease in the size of the liver metastasis (lower panels) compared with the baseline scan. The antitumour response was maintained for nearly 1 year. (**B**) A 64-year-old male with stomach cancer who was treated with NK105 at a dose level of 150 mg m^{-2}. Baseline scan (left panel) showing a peritoneal metastasis and liver metastasis. About 40% reduction (right panel) was observed in peritoneal metastasis, but not in the liver metastasis after fifth course.

Table 4 Pharmacokinetic parameters

	Dose (mg m^{-2})	*n*	C_{max} (μg ml^{-1})	$AUC_{0-inf.}$ (μg h^{-1} ml^{-1})	$t_{1/2}$ (h)	CL_{tot} (ml h^{-1} m^{-2})	V_{ss} (ml m^{-2})	UE (%)	CL_r (ml h m^{-2})
NK105	150	7	40.1699 ±5.5334	369.8 ±35.2	10.6 ±1.3	408.6 ±37.3	4527.1 ±639.5	5.3 ±1.5	21.6 ±6.5
PTX	210	5	6.744 ±2.733	23.18 ±10.66	13.3 ±1.5	10740 ±4860	58900 ±24700	9.45 ±3.76	1020 ±648
XYOTAX[a]	233	4	NA	1583 ±572	120 ±28	276 ±63	6200 ±2100	NA	NA
Abraxane	300	5	13.52 ±0.95	17.61 ±3.70	14.6 ±2.04	17700 ±3894	370000 ±85100	NA	NA
Genoxol-PM	300	3	3.107 ±1.476	11.58 ±4.28	11.4 ±2.4	29300 ±13800	NA	NA	NA

[a]Conjugated taxanes.

system. When compared with conventional PTX at a dose of 210 mg m^{-2} (conventional dose for a 3-week regimen in Japanese patients), NK105 at a dose of 150 mg m^{-2} (recommended phase II dose) exhibited more than 15-fold larger plasma AUC and a 26-fold lower CL_{tot}. The larger plasma AUC is consistent with the stability of the micelle formulation in plasma. The V_{ss} of NK105 was 13-fold lower than that of conventional PTX. This suggests that PTX may have a relatively lower distribution in normal tissue, including normal neural tissue, following NK105 administration. Regarding the drug distribution in tumours, nanoparticle drug carriers have been known to preferentially accumulate in tumour tissues utilising the EPR effect (Matsumura and Maeda, 1986;

Maeda *et al*, 2000; Duncan, 2003). We speculate that NK105 accumulates more in tumour tissues than free PTX, since NK105 is very stable in the circulation and exhibits a markedly higher plasma AUC than free PTX. Moreover, a polymeric micelle carrier system for a drug has the potential to enable the sustained release of the drug inside a tumour following the accumulation of micelles in the tumour tissue (Hamaguchi *et al*, 2005; Uchino *et al*, 2005; Koizumi *et al*, 2006). Regarding NK105 in particular, this sustained release may begin at a PTX-equivalent dose of $<1\,\mu g\,ml^{-1}$ (data not shown). Consequently, the released PTX is distributed throughout the tumour tissue where it kills the cancer cells directly.

In the present study, NK105 appeared to exhibit characteristic pharmacokinetics different from those of other PTX formulations including conventional PTX, Abraxane, Genexol-PM, and Xyotax. For example, previous clinical PK data at each phase II recommended dose shown that plasma AUC and C_{max} were 11.58 and 3.1 in Genexol-PM (Table 4). The antitumour activities seen in two patients with intractable cancers are encouraging. In addition, we recently demonstrated in preclinical study that combined NK105 chemotherapy with radiation exerts a significantly more potent antitumour activity, compared with combined PTX therapy and radiation (Negishi *et al*, 2006). This data on NK105 justifies its continued clinical evaluation.

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Clinical Studies

A phase I trial of S-1 with concurrent radiotherapy for locally advanced pancreatic cancer

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This study investigated the maximum tolerated dose of S-1 based on the frequency of its dose-limiting toxicities (DLT) with concurrent radiotherapy in patients with locally advanced pancreatic cancer. S-1 was administered orally at escalating doses from 50 to 80 mg m^{-2} b.i.d. on the day of irradiation during radiotherapy. Radiation therapy was delivered through four fields as a total dose of 50.4 Gy in 28 fractions over 5.5 weeks, and no prophylactic nodal irradiation was given. Twenty-one patients (50 three; 60 five; 70 six; 80 mg m^{-2} seven patients) were enrolled in this trial. At a dose of 70 mg m^{-2} S-1, two of six patients demonstrated DLT involving grade 3 nausea and vomiting and grade 3 haemorrhagic gastritis, whereas no patients at doses other than 70 mg m^{-2} demonstrated any sign of DLT. Among the 21 enrolled patients, four (19.0%) showed a partial response. The median progression-free survival time and median survival time for the patients overall were 8.9 and 11.0 months, respectively. The recommended dose of S-1 therapy with concurrent radiotherapy is 80 mg m^{-2} day^{-1}. A multi-institutional phase II trial of this regimen in patients with locally advanced pancreatic cancer is now underway.

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Pancreatic cancer (PC) is one of the leading causes of cancer death worldwide. The prognosis of patients with this disease remains extremely poor, with a 5-year survival rate after diagnosis of less than 5%. Despite recent improvements in diagnostic techniques, PC is diagnosed at an advanced stage in most patients. Among these patients, roughly one-third is diagnosed as having locally advanced disease radiographically confined to the pancreas and surrounding tissues. In patients with locally advanced PC, the concurrent external-beam radiation therapy and 5-fluorouracil (5-FU) therapy has been shown to offer a survival benefit in comparison with radiotherapy alone (Moertel *et al*, 1969, 1981) or chemotherapy alone (Gastrointestinal Tumor Study Group, 1988). In an attempt to improve the efficacy of 5-FU with concurrent radiotherapy, various anticancer agents and radiation schedules are being examined in clinical trials, but no significant impact on survival has been accomplished. Because of these results, 5-FU with concurrent radiotherapy remains the predominant chemoradiotherapy for locally advanced PC in clinical use (Willett *et al*, 2005; Yip *et al*, 2006).

S-1 is a novel orally administered drug, which is a combination of tegafur, 5-chloro-2,4-dihydroxypyridine and oteracil potassium in a 1:0.4:1 molar concentration ratio. Tegafur is hydroxylated and converted to 5-FU by the hepatic microsomal enzymes. 5-Chloro-2,4-dihydroxypyridine is a competitive inhibitor of dihydropyrimidine dehydrogenase, which is involved in the degradation of 5-FU, and acts to maintain effective concentrations of 5-FU in plasma and tumour tissues. Oteracil potassium, a competitive inhibitor of orotate phosphoribosyltransferase, inhibits the phosphorylation of 5-FU in the gastrointestinal tract, reducing the serious gastrointestinal toxicity associated with 5-FU (Shirasaka *et al*, 1996a). In athymic nude rats, S-1 has been shown to result in retention of a higher and more prolonged concentration of 5-FU in plasma and tumour tissues in comparison with 5-FU and uracil/tegafur (Shirasaka *et al*, 1996b). The antitumour effect of S-1 has already been demonstrated in a variety of solid tumours, including advanced gastric cancer (Sakata *et al*, 1998), colorectal cancer (Ohtsu *et al*, 2000), non-small-cell lung cancer (Kawahara *et al*, 2001), and head and neck cancer (Inuyama *et al*, 2001). In patients with metastatic PC, a recent early phase II study has demonstrated a response rate of 21% (Ueno *et al*, 2005), and a more favourable tumour response (response rate: 38%) and survival (median: 8.8 months) have been reported in a multi-institutional late phase II trial of S-1 (Furuse *et al*, 2005).

Thus, S-1 has promising antitumour activity against advanced PC, and is much more convenient to administer than intravenous 5-FU infusion, as it is taken orally. Concurrent radiotherapy along with S-1 therapy as an alternative to 5-FU infusion may result in more efficient treatment and improve the quality of life of patients. Therefore, we conducted a phase I trial to determine the maximum tolerated dose of S-1 with concurrent radiotherapy based on the frequency of dose-limiting toxicities (DLT) in patients with locally advanced PC.

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PATIENTS AND METHODS

Eligibility

Patients eligible for study entry had histologically or cytologically confirmed locally advanced nonresectable PC. Eligibility criteria were age 20–74 years; Karnofsky performance status 70–100 points; no evidence of distant metastasis; adequate oral intake; estimated life expectancy $\geqslant$12 weeks after study entry; no earlier treatment for PC; adequate haematological function (haemoglobin $\geqslant 10\,g\,dl^{-1}$, leucocytes $\geqslant 4000\,mm^{-3}$, neutrophils $\geqslant 2000\,mm^{-3}$ and platelets $\geqslant 100\,000\,mm^{-3}$); adequate hepatic function (serum total bilirubin $\leqslant$2.0 times upper normal limit (UNL); serum albumin $\geqslant 3.0\,g\,dl^{-1}$ and serum transaminases (aspartate aminotransferase (AST)/alanine aminotransferase (ALT)) $\leqslant$2.5 times UNL or $\leqslant$5 times UNL if biliary drainage present); adequate renal function (serum creatinine $\leqslant 1.0\,mg\,dl^{-1}$); written informed consent.

The exclusion criteria were watery diarrhoea; pleural effusion or ascites; active infection; active gastroduodenal ulcer; severe complication such as heart disease or renal disease; mental disorder; history of drug hypersensitivity; active concomitant malignancy; pregnant and lactating females; females of child-bearing age unless using effective contraception.

Ultrasonography, multidetector row-computed tomography of the abdomen and chest X-ray were performed for pretreatment staging to assess the local extension of the tumour and exclude the presence of distant metastasis. The computed tomography-based criteria for tumour nonresectability included tumour encasement of the celiac trunk, common hepatic artery, superior mesenteric artery or bilateral invasion of the portal vein. All patients with obstructive jaundice underwent percutaneous transhepatic or endoscopic retrograde biliary drainage before treatment. This phase I study was approved by the Institutional Review Board of the National Cancer Center and conducted in accordance with the Declaration of Helsinki Principles.

Treatment schedule

This was an open-label, two-institutional and single-arm phase I study that was performed on an in-patient basis. Radiotherapy was administered by 10 or 25 MV photons using three-dimensional treatment planning. A total dose of 50.4 Gy was delivered in 28 fractions over 5.5 weeks. The clinical target volume (CTV) included only the gross primary tumour and nodal involvement enlarged over 10 mm detected by computed tomography. Elective nodal irradiation was not used. The planning target volume was defined as CTV plus a 10 mm margin in the lateral direction and 10–20 mm margin in the craniocaudal direction to account for respiratory organ motion and daily set-up error. The four-field technique (anterior, posterior and opposed lateral fields) was used. There was no field reduction. The spinal cord dose was maintained below 45 Gy. The dose received by $\geqslant$50% of the liver was limited to $\leqslant$30 Gy, and that received by $\geqslant$50% of both kidneys was limited to $\leqslant$20 Gy.

S-1 was administered orally twice daily after breakfast and dinner on the day of irradiation (Monday to Friday) during radiotherapy. The initial dose of S-1 was $50\,mg\,m^{-2}\,day^{-1}$, and the dose was escalated to $80\,mg\,m^{-2}\,day^{-1}$ in increments of $10\,mg\,m^{-2}\,day^{-1}$ (Table 1). The calculated S-1 dose was rounded down to the nearest 60, 80, 100 or 120 mg. S-1 at $50\,mg\,m^{-2}\,day^{-1}$ is reported to be almost equivalent to $200\,mg\,m^{-2}\,day^{-1}$ intravenously 5-FU (Hirata *et al*, 1999), which has been used in protracted 5-FU infusion with concurrent radiotherapy for locally advanced PC at our institutions (Ishii *et al* 1997). S-1 at $80\,mg\,m^{-2}\,day^{-1}$ is the standard dose used as a single agent for systemic therapy (Furuse *et al*, 2005; Ueno *et al*, 2005). Patients maintained a daily journal to record their intake of S-1 and any signs or symptoms that they experienced.

Table 1 Dose schedules of S-1 with concurrent radiotherapy

Dosage level	S-1 dose ($mg\,m^{-2}\,day^{-1}$)	Number of patients
1	50	3
2	60	5
3	70	6
4	80	7

Patient cohorts had a minimum of three patients at each dose level. If no DLT was observed in the initial three patients, the dosage was escalated in successive cohorts. If DLT was observed in one or two of the initial three patients, three additional patients were evaluated at that dose level. If only one or two of six patients experienced DLT, dose escalation was continued. However, if three or more patients experienced DLT at a given dose level, then the previous dose level was considered as the maximum tolerated dose. Dose-limiting toxicities was defined as the following manifestations of toxicity observed until completion of chemo-radiotherapy: grade 3 leucocytopenia and/or neutropenia with a fever $\geqslant$38°C lasting 3 days or more, grade 3 leucocytopenia and/or neutropenia with infection, grade 4 leucocytopenia and/or neutropenia lasting 3 days or more, grade 4 leucocytopenia and/or neutropenia requiring haematopoietic colony-stimulating factors, platelets $<25\,000\,mm^{-3}$, grade 3 thrombocytopenia requiring transfusion, serum AST/ALT $\geqslant$10 times UNL, grade 3 or 4 nonhaematological toxicities excluding nausea, vomiting, anorexia, fatigue, constipation, hyperglycaemia, and abnormality of sodium, potassium, and calcium or treatment interruption for longer than 12 days.

When grade 3 or greater haematological toxicity, total bilirubin level 2.0–3.0 times UNL, serum AST/ALT 5.0–10.0 times UNL, grade 3 vomiting and/or grade 2 nonhaematological toxicity excluding nausea, vomiting, anorexia, fatigue, constipation, alopecia and pigmentation change, were observed, radiotherapy and S-1 administration was suspended. Treatment was resumed when the toxicities were resolved by one grade or more, compared with these suspension criteria. Dose modification was not performed in this study. When DLT or tumour progression was observed during chemoradiotherapy, this treatment was discontinued. After this treatment, the patients were allowed to receive another anticancer treatment at their physician's discretion.

Toxicity and response evaluation

The primary end point of this trial was to evaluate the frequency of DLT, and the secondary end point was to evaluate the potential antitumour activity. Treatment-related toxicities were assessed using the National Cancer Institute Common Toxicity Criteria version 2.0. During this treatment, complete blood count with differentials, serum chemistry and urinalysis were carried out at least once a week. Tumor response was evaluated at the completion of chemoradiotherapy and every 8 weeks thereafter until tumour progression, according to the Japan Society for Cancer Therapy criteria (Japan Society for Cancer Therapy, 1993) as follows: a complete response was defined as the disappearance of all clinical evidence of the tumour for a minimum of 4 weeks. A partial response was defined as a 50% or greater reduction in the sum of the products of two perpendicular diameters of all measurable lesions for a minimum of 4 weeks. A minor response was defined as a 25% or greater reduction and less than 50% in the sum of the products of two perpendicular diameters of all measurable lesions for a minimum of 4 weeks or a 50% or greater reduction in the sum of the products of two perpendicular diameters of all measurable lesions lasting less than 4 weeks. No change was defined as a reduction of less than 25% or a less than 25% increase

in the sum of the products of two perpendicular diameters of all lesions for a minimum of 4 weeks. Progressive disease was defined as an increase of 25% or more in the sum of the products of two perpendicular diameters of all lesions, or the appearance of any new lesion. Progression-free survival time was defined as the time from the date of initial treatment to the first documentation of progression or death. Overall survival was measured from the date of initial treatment to date of death or the date of the last follow-up. Progression-free and overall survival times were calculated by the Kaplan–Meier method. Serum carcinoembryonic antigen (CEA) levels and serum carbohydrate antigen 19-9 (CA19-9) levels were measured at least every 8 weeks by a radioimmunometric assay using the Centocor radioimmunoassay kit (Centocor Inc., Malvern, PA, USA).

RESULTS

Patient characteristics

Twenty-one patients were enrolled in this study from May 2004 and November 2005 at the National Cancer Center Hospital, Tokyo, and the National Cancer Center Hospital East, Kashiwa, Chiba, Japan. The characteristics of the patients are listed in Table 2. The median age was 59 years (range: 51–74). Karnofsky performance status was 100 in 12 patients (57%), 90 in 8 (38%) and 80 in one (5%). The median maximum tumour size was 37 mm (range: 25–60), and the median planning target volume was 265 cm^3 (range: 153–408). The causes of the unresectable PCs were invasion of the celiac trunk in nine patients, invasion of the superior mesenteric artery in eight patients and invasion of both regions in four patients. Patients were treated with S-1 and concurrent radiation over four dose levels, as listed in Table 1. After completion of chemoradiotherapy, 20 patients (95%) received gemcitabine alone for their cancer until disease progression, and one patient received the other treatment at another hospital.

Table 2 Patient characteristics

Characteristics	Number of patients	%
Age (years)		
Median	59	
Range	51–74	
Gender		
Male	9	43
Female	12	57
Karnofsky performance status		
100	12	57
90	8	38
80	1	5
Tumour location		
Head	13	62
Body-tail	8	38
Maximum tumour size (mm)		
Median	37	
Range	25–60	
CEA (ng/ml)		
Median	4.5	
Range	1.0–75.0	
CA19-9 (U/ml)		
Median	759	
Range	1–6,300	

CEA = carcinoembryonic antigen; CA19–9 = carbohydrate antigen 19–9.

Toxicity

The toxicities observed in the 21 enrolled patients are listed in Table 3. With regard to overall haematological toxicity, grade 3 neutropenia was observed in only one patient at the dose of level 1, and other grades 3–4 toxicities were not observed. For non-haematological toxicity, grade 3 anorexia and nausea (three patients), grade 3 vomiting (one patient) and grade 3 haemorrhagic gastritis (one patient) occurred at level 3, and grade 3 AST elevation was observed in a patient at level 4. As a late toxicity, duodenal ulcer with epigastralgia was observed in one patient at level 3 (S-1 70 mg m^{-2}) 8 months after chemoradiotherapy, requiring embolisation of the gastroduodenal artery to treat severe bleeding from the ulcer and a 2-month hospital stay. No other grades 3–4 nonhaematological toxicities or treatment-related deaths occurred in this study. Treatment was suspended in four patients (level 2, one; level 3, two; level 4, one patient) because of obstructive jaundice (two patients) or grade 3 anorexia (two patients); the durations of S-1 dose withholding were 3, 12, 2 and 13 days, respectively. One patient with grade 3 anorexia (level 3) was unable to resume this treatment. The compliance rate of the patients taking S-1 was as high as 99% (1170/1176 doses).

There was no occurrence of DLT at the dose of levels 1 or 2, but two of six patients who received a level 3 dose experienced DLT; one of these patients required suspension of treatment for more than 12 days due to grade 3 anorexia, nausea and vomiting after the third fraction of chemoradiotherapy, and a second developed grade 3 haemorrhagic gastritis after completion of 13 fractions. However, no DLT at a dose of level 4 was observed, and S-1 at 80 mg m^{-2} with concurrent radiotherapy was considered to be well-tolerated.

Five patients (level 2, two; level 3, two; level 4, one) of the 21 who were enrolled had to abandon this treatment. Two patients at level 2 developed massive ascites and infarction of the cerebellum, respectively, during chemoradiotherapy. The cause of the massive ascites was disease progression, as cancer cells were confirmed in the ascitic fluid. The cerebellar infarction was considered to have been unrelated to the treatment, because the patient had a history of the same problem. Two patients at level 3 had to discontinue the treatment because of DLT according to the protocol, and one patient at level 4 decided to stop the treatment, despite lack of severe toxicity, at her own request.

Efficacy

All the patients were included in the response evaluation. Four patients (levels 1 and 2, 0; level 3, one; level 4, three) achieved a partial response, giving an overall response rate of 19% (95% confidence interval, 5–42%). Four patients (19%) showed a minor response, and nine (43%) and three patients (14%) had no change and progressive disease, respectively. Tumor response could not be evaluated in one patient (5%), because she was transferred to another hospital to seek some other treatment for her PC. None of the patients' conditions improved to resectable or operable diseases after the completion of treatment. After the start of chemoradiotherapy, the serum CA19-9 level was reduced by more than 50% compared to the pretreatment level in 14 (88%) of 16 patients who had shown a pretreatment level of 100 U/ml or greater, and the serum CEA level was reduced by more than 50% relative to the pretreatment level in three (100%) of three patients who had a pretreatment level of 10 ng ml^{-1} or greater. Eighteen of the 21 patients had disease progression at the time of analysis. The pattern of disease progression was distant metastases in 11 (52%), deterioration of general condition in five (24%) and locoregional recurrence in two patients (10%). The median progression-free survival time for all patients was 8.9 months (Figure 1). At the time of analysis, 13 patients had died due to tumour progression. The median survival time and 1-year survival rate for patients as a whole were 11.0 months and 42.9%, respectively (Figure 1).

Table 3 Toxicity

	Number of patients											
	Level 1 ($n=3$)			Level 2 ($n=5$)			Level 3 ($n=6$)			Level 4 ($n=7$)		
Grade	1,2	3	4	1,2	3	4	1,2	3	4	1,2	3	4
Leucocytes	3	0	0	3	0	0	3	0	0	6	0	0
Neutrophiles	1	1	0	1	0	0	2	0	0	3	0	0
Haemoglobin	0	0	0	2	0	0	1	0	0	4	0	0
Platelets	0	0	0	1	0	0	1	0	0	2	0	0
Anorexia	2	0	0	3	0	0	1	3	0	5	0	0
Nausea	0	0	0	2	0	0	1	3	0	6	0	0
Vomiting	1	0	0	0	0	0	2	1	0	3	0	0
Diarrhoea	1	0	0	0	0	0	0	0	0	0	0	0
Mucositis	0	0	0	0	0	0	0	0	0	0	0	0
Fatigue	2	0	0	2	0	0	2	0	0	2	0	0
Gastritis	0	0	0	0	0	0	0	1	0	0	0	0
Duodenal ulcer	0	0	0	0	0	0	0	1	0	0	0	0
Bilirubin	1	0	0	0	0	0	0	0	0	0	0	0
Hypoalbuminaemia	1	0	0	1	0	0	3	0	0	5	0	0
AST	1	0	0	1	0	0	4	0	0	2	0	0
ALT	1	0	0	0	0	0	3	0	0	1	1	0
Alkaline phosphatase	0	0	0	0	0	0	1	0	0	2	0	0
Creatinine	0	0	0	0	0	0	1	0	0	0	0	0

AST = aspartate aminotransferase; ALT = alanine aminotransferase.

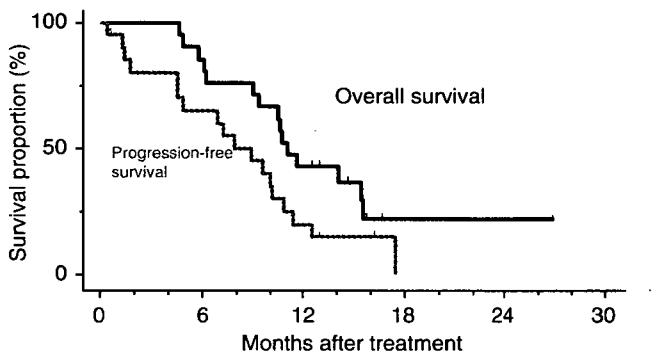

Figure 1 Overall survival and progression-free survival curves of 21 patients who received S-1 with concurrent radiotherapy for locally advanced pancreatic cancer. Tick marks indicate censored cases.

DISCUSSION

On the basis of results of previous randomised controlled trials (Moertel *et al*, 1969, 1981; Gastrointestinal Tumor Study Group, 1988), the combination of 5-FU therapy and radiotherapy has become a frequently employed treatment for locally advanced PC (Willett *et al*, 2005; Yip *et al*, 2006). Because of the modest survival benefit of 5-FU-based chemoradiotherapy, numerous investigators are pursuing phase I and II trials of radiotherapy with new chemotherapeutic agents such as gemcitabine, paclitaxel, capecitabine, bevacizumab, gefitinib and erlotinib (Blackstock *et al*, 2003; Okusaka *et al*, 2004; Rich *et al*, 2004; Crane *et al*, 2006; Czito *et al*, 2006). However, no marked improvement of survival has been observed. S-1 is an oral fluoropyrimidine derivative that has demonstrated excellent efficacy with mild toxicity in patients with metastatic PC (Furuse *et al*, 2005). It is considered to be beneficial because of its convenience of being administered by the oral route. In addition, combined S-1 and radiotherapy has been demonstrated to exert a synergistic effect against 5-FU-resistant cancer xenografts (Harada *et al*, 2004; Nakata *et al*, 2006). Therefore, a clinical trial of concurrent radiotherapy with S-1 therapy for locally advanced PC was designed to intensify the treatment efficacy and improve the convenience of administration.

In this study, a limited radiation field, of which the planning target volume included only the gross tumour volume without prophylactic nodal irradiation, was adopted to minimise the volume of normal tissue treated, because our retrospective study showed that a larger planning target volume for irradiation was the significant predictor of severe acute gastrointestinal toxicity in patients treated with chemoradiotherapy (Ito *et al*, 2006). A similar radiation field has been attempted in recent reported trials of chemoradiotherapy to decrease the degree of gastrointestinal toxicity (Muler *et al*, 2004; Crane *et al*, 2006). Gastrointestinal toxicities, such as anorexia, nausea and vomiting, are major troublesome adverse events during chemoradiotherapy, necessitating intravenous fluid infusion and sometimes discontinuation of chemoradiotherapy (Talamonti *et al*, 2000; Crane *et al*, 2002; McGinn and Zalupski, 2003; Okusaka *et al*, 2004). In the present study, some gastrointestinal toxicities were observed, but were easily managed. Moreover, the limited radiation field used in this study did not result in excess failures in the border of radiation field, because locoregional recurrence was observed in only two patients of this series.

In this study, DLT was observed in only two patients at level 3 (S-1 70 mg m^{-2}). The DLT in the first patient was grade 3 anorexia, nausea and vomiting, requiring suspension of treatment for longer than 12 days, and the second DLT was grade 3 haemorrhagic gastritis. Other than DLT toxicity, acute grades 3–4 toxicities during chemoradiotherapy were observed in only three patients: grade 3 neutropenia, grade 3 anorexia and nausea, and grade 3 AST elevation in one patient each. As a late toxicity, duodenal ulcer was observed 8 months after treatment in one patient at level 3, but no other late toxicity occurred. Accordingly, S-1 at a daily dose of 80 mg m^{-2} (level 4) was considered to be well tolerated, and this dose was deemed recommendable.

In patients with locally advanced PC who are receiving chemoradiotherapy, it is important to enhance local control while simultaneously reducing the risk of distant metastases. In concurrent gemcitabine-based chemoradiotherapy, both full-dose gemcitabine and standard-dose radiotherapy are difficult to administer because of their associated toxicities (Crane *et al*, 2002; Blackstock *et al*, 2003; McGinn and Zalupski, 2003; Okusaka

et al, 2004). In contrast, in the present trial, the combination of full-dose S-1 ($80\,mg\,m^{-2}$) and standard-dose radiotherapy (50.4 Gy/28 fractions) was easy to administer and had favourable toxicity profiles. Therefore, this regimen might have a dual benefit of counteracting systemic tumour spread as well as acting as a potent radiosensitizer for local control. With regard to the antitumour activity of this treatment, four (19%) of the 21 patients achieved a partial response, and the response rate at the recommended dose was 43% (3/7). The progression-free survival time (median: 8.9 months) and overall survival time (median: 11.0 months) were also favourable as a phase I trial. In this study, many patients (95%) received gemcitabine alone after completion of this regimen. Such adjuvant gemcitabine therapy might influence the efficacy of treatment, although the extent of its impact on tumour response and survival has not been fully elucidated in patients with locally advanced PC. Since both the efficacy and toxicity profile of this regimen appear to be attractive, a phase II trial is required to clarify the antitumour activity, survival and toxicity of S-1 $80\,mg\,m^{-2}\,day^{-1}$ with concurrent radiation therapy for locally advanced PC.

In conclusion, the recommended dose of S-1 with concurrent radiotherapy is $80\,mg\,m^{-2}\,day^{-1}$ on the day of irradiation, and this regimen has a mild toxicity profile while delivering substantial antitumour activity for patients with locally advanced PC. Orally administered S-1 may offer an easy alternative to intravenous 5-FU without impairing the quality of life. A phase II trial of S-1 at the optimal dose of $80\,mg\,m^{-2}\,day^{-1}$ with concurrent radiation in patients with locally advanced PC is now underway in a multi-institutional setting.

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How I do it

Wrapping of skeletonized and divided vessels using the falciform ligament in distal pancreatectomy

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Abstract

Background: A pancreatic fistula is a major cause of morbidity in patients undergoing distal pancreatectomy (DP). A pancreatic fistula may expose skeletonized or divided vessels directly to pancreatic juice, creating a setting for vessel erosion and delayed intra-abdominal hemorrhage (DIH). With the aim of protecting vessels near the pancreatic stump from potential pancreatic fistulas, we have adopted a surgical option by which these vessels are wrapped using a pedicled falciform ligament.

Methods: After completing DP, the pedicled falciform ligament is spread out widely on major vessels exposed during resection near the pancreatic stump, and fixed to the surrounding retroperitoneal connective tissue. These procedures allow the complete separation of these vessels from the pancreatic stump. We reviewed the cases of 8 patients who underwent DP including these procedures.

Results: The mobilization of the falciform ligament and the wrapping of the vessels were successfully performed without any complications. Although 2 patients (14.5%) developed pancreatic fistulas, DIH did not occur in any of the patients.

Conclusions: The wrapping of the skeletonized and divided vessels using a pedicled falciform ligament is simple and easy, and may be an effective prophylactic measure against DIH following DP.

Keywords: Pancreatic fistula; Delayed intra-abdominal hemorrhage; Distal pancreatectomy; Falciform ligament

Pancreatic fistula is a common complication of distal pancreatectomy (DP) [1]. The incidence of pancreatic fistula after DP ranges from 5% to 60% [2–15]. Even recent advances in medical and surgical care of DP cannot completely eliminate the possibility of pancreatic fistula development [3,6,8,13,14,16]. A pancreatic fistula exposes skeletonized or divided vessels directly to pancreatic juice and/or intraperitoneal abscess, creating a setting for vessel erosion and lethal delayed intra-abdominal hemorrhage (DIH) [17,18]. The incidence of DIH after DP ranges from 2% to 4% [7,19]. Taken together, these reports suggest that the protection of these vessels from pancreatic fistulas may be envisaged as a prophylactic measure against DIH after DP. With the aim of protecting vessels near the pancreatic stump from a potential pancreatic fistula, we have adopted a surgical option by which these vessels are wrapped using the pedicled falciform ligament. This surgical option is simple and easy, and appears to minimize the incidence of DIH after DP. Herein, we present our novel procedure and the preliminary results of 8 patients who underwent DP employing this option.

Patients and Methods

Surgical techniques for mobilization of the falciform ligament and the wrapping of vessels

A pedicled falciform ligament is easily and rapidly obtained during a midline abdominal incision. After incising the linea alba, the preperitoneal fat is bluntly dissected to the right prior to incising the peritoneum. The falciform ligament is mobilized by dividing it near the umbilicus and incising its anterior peritoneal reflections along the posterior right rectus sheath. An additional length can be obtained by continuing the anterior incision cephalad to the undersurface of the diaphragm and to the triangular ligament, then incising the posterior peritoneal reflections cephalad to the

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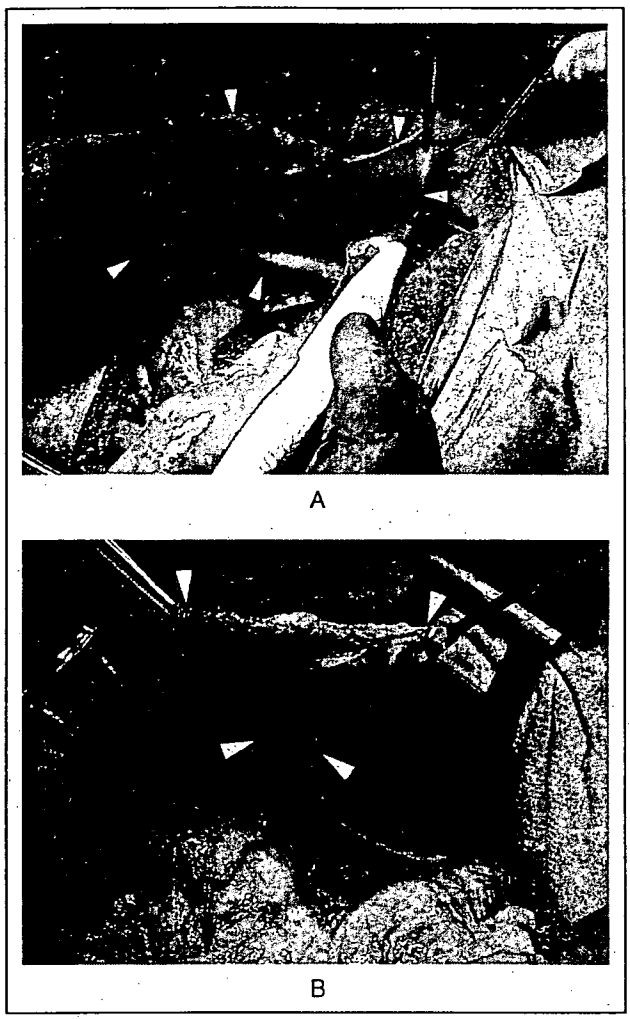

Fig. 1. (A) The mobilization of the falciform ligament (*arrowheads*). (B) The pedicled falciform ligament (*arrowheads*).

anterior surface of the liver to the triangular ligaments (Fig. 1A) [20]. The pedicled falciform ligament (Fig. 1B) will usually reach the space of the pancreatic stump and the splanchnic vessels exposed during resection. After completing DP, the pedicled falciform ligament is perineally brought through a newly opened hole in the lesser omentum to the pancreatic stump area. Then it is spread out widely on the vessels near the pancreatic stump, such as the common hepatic artery, superior mesenteric vein, portal vein, and stumps of the splenic artery/vein (Fig. 2A), and fixed with interrupted 3-0 silk sutures to the surrounding retroperitoneal connective tissue (Fig. 2B). These procedures allow the complete separation of the vessels from the pancreatic stump (Fig. 2B).

Patients and DP procedures

Between September 2003 and November 2005, eight patients underwent DP employing the wrapping of the vessels using the pedicled falciform ligament. The patients were 4 men and 4 women with a mean age of 68 years (range 41 to 76 years). The indications for DP included ductal adenocarcinoma (n = 2), intraductal papillary mucinous adenocarcinoma (n = 1), and intraductal papillary mucinous adenoma (n = 5). A concomitant splenectomy was carried out in all 8 patients.

During DP, lymph nodes around the common hepatic artery were dissected. The splenic artery and vein were divided at their origin. Therefore, the skeletonized common hepatic artery, stumps of the splenic artery/vein and, occasionally, the superior mesenteric vein and/or portal vein were exposed near the pancreatic stump. The pancreas was transected at the level of the superior mesenteric vein. Five patients had a stapled closure of the pancreatic stump. Stapled transection was achieved using an Auto Suture ENDO-UNIVERSAL-clip-instrument (United States Surgical Corporation, Norwalk, CT). In the other 3 patients, during the pancreatic transection, the pancreatic parenchyma was divided using an electrocautery or a surgical scalpel (electrocautery: 2, scalpel: 1). In these cases, the main pancreatic

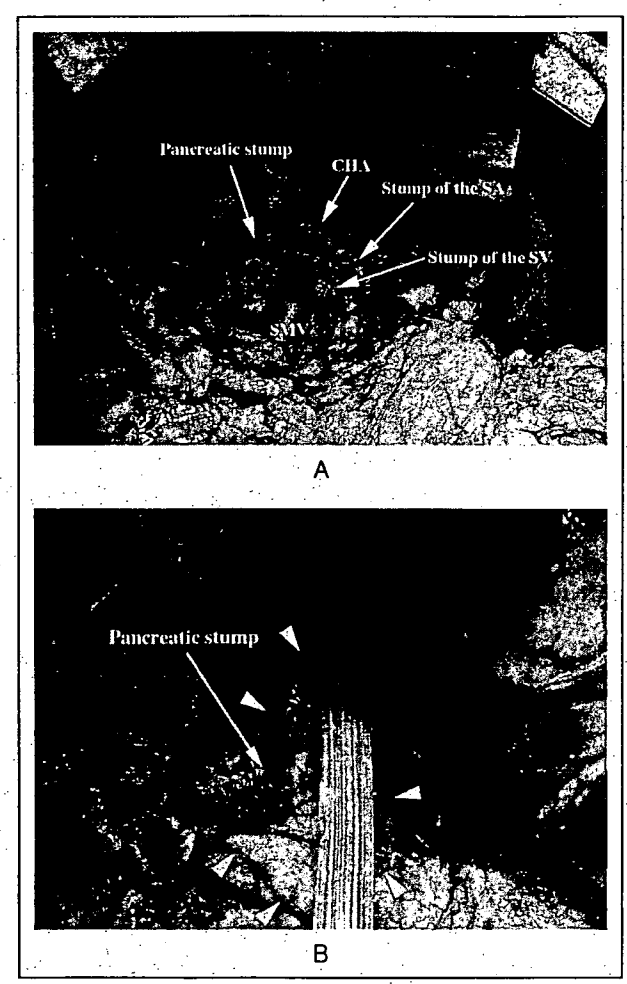

Fig. 2. (A) The wrapping of the vessels using the pedicled falciform ligament. Surgical view before the wrapping of the pedicled falciform ligament. The common hepatic artery, stump of the splenic artery, stump of the splenic vein, superior mesenteric vein, and portal vein are exposed near the pancreatic stump. CHA, common hepatic artery; SA, splenic artery; SV, splenic vein; SMV, superior mesenteric vein. (B) Surgical view after the wrapping of the pedicled falciform ligament (*arrowheads*). This procedure allows the complete separation of the vessels from the pancreatic stump. A closed suction drain (silicone rubber drain) was placed adjacent to the pancreatic stump and fixed to the pedicled falciform ligament.

duct was ligated with a nonabsorbable suture, and the stump of the pancreas was left open. Fibrin glue was not applied to the stump in any of the patients. A closed suction drain was placed adjacent to the pancreatic stump and fixed with an absorbable suture to the falciform ligament (Fig. 2B). Octreotide was not administered postoperatively.

A pancreatic fistula is defined as a biochemical leakage in the presence of clinical sequelae, such as the saponification of drainage fluid, fever or leucocytosis, intra-abdominal abscess formation, and the need for percutaneous drainage or reoperation [15]. A biochemical leakage is defined as an amylase level in drainage fluid that is more than 4-fold the upper limit of the normal serum amylase level on postoperative day 3 or 5 [15].

Results

The mobilization of the falciform ligament and the wrapping of the vessels were successfully performed without any complications. At the end of the operation, none of the patients experienced ischemia in the pedicled falciform ligament. The mean operating time and blood loss were 228 (range 181 to 344) minutes and 218 (range 55 to 511) mL, respectively.

Pancreatic fistula occurred in 2 patients (14.5%), both associated with bacterial infection. The pancreatic fistulas resolved spontaneously by 32 days after conservative treatments including pancreatic rest and/or intermittent local irrigation with saline via the drain. These were then closed with no additional serious conditions related to the fistula, such as DIH, pseudocyst formation, and sepsis. The drain was removed on postoperative day 7 in patients with no evidence of pancreatic fistula. Complications associated with the drain removal did not occur in any case. There were no postoperative deaths.

Comments

Most pancreatic fistulas after DP usually resolve spontaneously, albeit over a long period, after conservative treatments including pancreatic rest (no oral intake with total parenteral nutrition or octreotide administration) and adequate drainage (drains placed during the initial operation or postoperatively via the percutaneous approach) [21–23]. However, some patients with pancreatic fistulas develop complications, such as intraperitoneal abscess, sepsis, and lethal DIH [7]. Although the incidence (2% to 4%) of DIH after DP [7,19] is lower than that (2% to 8%) after pancreatoduodenectomy [17,24–28], preventing DIH associated with pancreatic fistula is an important step toward improving the short-term outcome after DP.

The prevention of DIH is also a major concern in pancreatoduodenectomy. The preferred surgical option for the prevention of DIH after pancreatoduodenectomy is the protection of the skeletonized or divided vessels from intra-abdominal complications, such as pancreatic fistula and intra-abdominal infection [18,24,29,30]. Indeed, the placement of the omental flap between these vessels and the pancreaticojejunostomy is successful for reducing the incidence of DIH after pancreatoduodenectomy (0% to 1%) [18,24]. These data support the idea that the protection of vessels could also be a measure against DIH following DP. For this purpose, the use of the omental flap in DP may be as good as those previously reported for pancreatoduodenectomy [18,24,29,30]. However, an adequate omentum is not available in some patients [20]. Complications of the use of the omental flap, such as intestinal obstruction, the total necrosis of the flap, and infection, have been reported [24]. Therefore, we consider the falciform ligament an excellent alternative to the omentum for the protection of vessels.

The falciform ligament is the obliterated umbilical vein (ligamentum teres or round ligament) and its encompassing parietal peritoneum. The pedicled falciform ligament, when adequately mobilized, is a large (15 cm to 30 cm) autologous tissue that will usually reach any surgical area in the upper abdomen. Although its availability is not widely appreciated, it has been used in several abdominal operations including those for hepatic injury [20], perforated gastroduodenal ulcer [31], and hiatal herniorrhaphy [32]. The use of the falciform ligament in DP has not been described [33].

The presented surgical option is a simple and easy technique for the complete separation of the vessels from the pancreatic stump. It is suggested that the falciform ligament can prevent the diffusion of pancreatic juice with or without bacterial infection and protect the vessels. In this study, none of the patients developed DIH. However, it could not be confirmed whether the present surgical option itself prevented DIH. Further controlled randomized studies involving large numbers of patients are warranted to confirm the value of the present surgical option.

In conclusion, the present surgical option (the wrapping of the vessels using the pedicled falciform ligament) is technically easy, and we believe that this may prevent DIH caused by a pancreatic fistula following DP.

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Combined vascular resection in operative resection for hilar cholangiocarcinoma: Does it work or not?

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Background. *It is still not clear how combined vascular resection affects the outcome of patients with hilar cholangiocarcinoma. Our aim was to evaluate implications of combined vascular resection in patients with hilar cholangiocarcinoma by analyzing the outcomes of all patients who underwent operative resection.*

Methods. *A total of 161 of 228 consecutive patients with hilar cholangiocarcinoma underwent bile duct resection with various types of hepatectomy (88%) and pancreaticoduodenectomy (4%). Combined vascular resection was carried out in 43 patients. Thirty-four patients had portal vein resection alone, 7 patients had both portal vein and hepatic artery resection, and 2 patients had right hepatic artery resection only. The outcomes were compared between the 3 groups: the portal vein resection alone (34), hepatic artery resection (9), and non-vascular resection (118).*

Results. *Histologically-positive tumor invasion to the portal vein beyond the adventitia was present in 80% of 44 patients undergoing combined portal vein resection. Operative mortality occurred in 11 (7%) patients. The survival rates of the non-vascular resection group were better than that of the portal vein resection alone and the hepatic artery resection groups: 1, 3, and 5 years after curative resection, 72%, 52%, and 41% versus 47%, 31%, and 25% ($P < .05$), and 17%, 0%, and 0% ($P < .0001$), respectively. Multivariate analysis showed 4 independent prognostic factors of adverse effect on survival after operation; operative curability, lymph node metastases, portal vein resection, and hepatic artery resection.*

Conclusions. *Although both portal vein and hepatic artery resection are independent poor prognostic factors after curative operative resection of locally advanced hilar cholangiocarcinoma, portal vein resection is acceptable from an operative risk perspective and might improve the prognosis in the selected patients, however, combined hepatic artery resection can not be justified. (Surgery 2007;141:581-8.)*

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HILAR CHOLANGIOCARCINOMA remains difficult to resect with curative intent despite the recent evolution and improvement of preoperative diagnostic imaging and operative techniques in hepatic resection. The resection rate is reported to be less than 40%, and curative resection with negative operative margin has been carried out in 15% to 83% of resected patients.[1] The importance of a negative operative margin for long-term survival has been confirmed by the results of several studies reported previously.[2-4] The reasons for irresectability in most patients with hilar cholangiocarcinoma are local extensive invasion to major vessels, such as the hepatic artery and the portal vein, and distant metastases, including peritoneal dissemination, liver metastases, distant lymph nodal metastases, and extra-abdominal metastases. The anatomic features of the hepatic hilus often make it easy for hilar cholangiocarcinoma to invade major vessels, such as those mentioned above. Therefore, hilar cholangiocarcinoma occasionally requires combined vascular resection and reconstruction, to obtain,

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negative resection margin due to involvement of hilar vasculatures, despite the fact that most patients with hilar cholangiocarcinoma are resected with unilateral hepatic lobectomy.

Several previous reports have described combined vascular resection in patients with hilar cholangiocarcinoma.[4-8] There is no general consensus, however, on the criteria for resectability of hilar cholangiocarcinoma involving the portal vein and the hepatic artery that requires combined vascular resection and reconstruction for the purpose of obtaining a cancer-free resection margin. Jarnagin et al[9] reported that encasement or occlusion of the main portal vein proximal to its bifurcation is one of criteria for irresectability in patients with cholangiocarcinoma. We have resected hilar cholangiocarcinoma involving the portal vein and the hepatic artery aggressively with combined vascular resection. In this study, our aim was to evaluate whether or not combined vascular resection of hilar cholangiocarcinoma is beneficial.

PATIENTS AND METHODS

Patients. Between january 1981 and March 2004, 204 patients with hilar cholangiocarcinoma were evaluated for resection at our institution; 187 patients underwent exploration for the purpose of potentially curative resection of whom 161 were resected. Pathologic tumor staging was carried out according to the UICC classification.[10]

Preoperative clinical assessment, as well as a laboratory and imaging workup including ultrasonography, magnetic resonance cholangiopancreatography (MRCP), cholangiography through the percutaneous transhepatic or endoscopic retrograde approaches, contrast-enhanced computed tomography (CT), and selective angiography, were carried out to establish the nature and extent of the disease and to define ductal and vascular anatomic details. All patients also underwent other generalized preoperative tests to assess their operative fitness. Preoperative portal embolization was carried out 14 to 22 days before operation in 16 patients in whom the remnant liver volume after operative resection was expected to be less than 40% of the expected whole liver volume from 1994 onward. The portal venous branch was embolized via the ileocolic vein, after mini-laparotomy under lumbar anesthesia. Of 161 resected patients, 149 underwent preoperative biliary drainage via a percutaneous transhepatic or an endoscopic retrograde transpapillary route for relief of obstructive jaundice and for correct evaluation of biliary lesion. Our criteria of irresectability defined by local, tumor-related factors were as follows: (1) tumor extension to bilateral secondary biliary radicles, except the caudate bile duct branches; (2) tumor extension to bilateral secondary portal vein branches; (3) tumor extension to bilateral secondary hepatic artery branches; and (4) expected remnant liver volume less than 30% of the whole liver volume We also evaluated age, gender, preoperative biliary drainage, and preoperative serum total bilirubin concentrations. Resected neoplasms were evaluated histologically as to operative margin, tumor size, tumor differentiation, nodal metastases, lymphatic vessel invasion, venous invasion, and T stage. In the patients with combined vascular resection, the extent of tumor invasion to the walls of the portal vein and the hepatic artery were also evaluated histologically. The 161 resected patients were stratified into 3 groups for evaluation of the efficacy of combined vascular resection in treatment of hilar cholangiocarcinoma: a portal vein resection alone group (n = 34), a hepatic artery resection group (n = 9), and a non-vascular resection group (n = 118). Postoperative complications and survival were analyzed in each of the 3 groups. In the same period, we managed 67 patients with unresectable hilar cholangiocarcinoma. The criteria for irresectability were, as described above, local tumor related factors and distant metastases. Unresectable patients underwent biliary drainage by percutaneous transhepatic or endoscopic nasobiliary routes, and were treated by biliary stenting with metallic or plastic endoprosthesis. In this series over a 24-year period, the management plan has not been changed except for the introduction of preoperative portal vein embolization from 1994 and of parenchyma-preserving hepatectomy[4] from 1990.

Operative procedures. Operative procedures were selected according to tumor extent in the bile duct, portal vein, and hepatic artery as determined by preoperative and intraoperative evaluation (Table I). Curative resection was defined as histologically negative operative margins at the hepatic stump of the bile duct, duodenal stump of the bile duct, and excisional surface. As reported previously,[4,11] parenchyma-preserving segment I hepatectomy and resection of segments I and IV were selected to limit resection as much as possible to what was necessary for curative purposes, especially in patients with comorbid medical conditions indicating increased operative risk (for example, advanced age, diabetes mellitus, liver dysfunction, and combined pancreaticoduodenectomy). Combined vascular resection was carried out in 43 of 161 resected patients; 34 patients had portal resection, 7 patients both portal vein and hepatic artery resection, and 2 patients only right hepatic artery

Table I. Operative procedures for hilar cholangiocarcinoma

	Patients (n)	%
Hilar bile duct resection	20	12
Hepatectomy	141	88
S_1^*-resection	14	9
$S_1 + S_4$ resection	10	6
Central bisegmentectomy	1	0.6
Extended left hepatectomy	52	32
Left trisegmentectomy	7	4
Extended right hepatectomy	50	31
Right trisegmentectomy	7	4
Total	161	100

*S, Hepatic segments were described according to the classification of Couinaud.

Table II. Vascular reconstruction in combined vascular resection

Vessels	*Patients (n)*
Portal vein	41
End to end	39
Autologous vein graft	2
Hepatic vein and inferior vena cava	5
Primary closure	3
Autologous vein graft	2
Hepatic artery	9
Reconstruction	
Left hepatic artery	3
Right hepatic artery	3
No reconstruction	
Right anterior hepatic artery	1
Right hepatic artery	1
Left hepatic artery	1

resection (Table II). The decision for combined vascular resection was made by the intra-operative macroscopic findings of tumor invasion to the vessels in conjunction with the preoperative imaging. The portal vein was reconstructed in an end-to-end fashion in 39 patients (95%), and autologous vein grafts, using a left renal vein,[12] in 2 patients. The hepatic artery was reconstructed in 6 patients in an end-to-end fashion.

Pancreaticoduodenectomy was carried out in 7 patients, including 4 patients in non-vascular resection group, 2 patients in portal vein resection group, and 1 patient in both portal vein and hepatic artery resection group. All operative procedures included resection of the extrahepatic duct and gallbladder with bilioenteric anastomosis using a Roux-en-Y jejunal loop. Biliary stent tubes were placed for bilioenteric anastomosis through a retrograde transhepatic route at the time of operation, and removed 3 to 4 weeks postoperatively. No adjuvant chemotherapy was given to patients who underwent resection. The 13 patients in whom the bile duct stump was a positive underwent external radiation treatment. No aggressive chemotherapy was given during any of the observation periods to patients who had undergone resection. The patency of reconstructed blood vessels was evaluated by Doppler ultrasonography and contrast-enhanced CT during the short-term and long-term follow-up.

Statistical analysis. Statistical analysis of patient survival was carried out according to the Kaplan-Meier method. Comparison of patient survival in the different groups was carried out using the log-rank test. Survival analyses were conducted according to various procedures and in regard to tumor characteristics, and operative and postoperative deaths. Pairwise comparisons among the 3 groups in regard to patient characteristics, operative features, operative curability, histopathologic features, operative morbidity, and mortality rates were analyzed by Mann-Whitney U and χ^2 tests for continuous and discontinuous variables, respectively. We used log-rank tests in univariate analyses to determine whether there were significant differences between subgroups. Multivariate regression analysis of factors related to outcomes was carried out using the Cox proportional hazard model. Significance was established at P less than .05. Statistical calculations were carried out with the use of SPSS software (SPSS, Inc., Chicago, Ill).

RESULTS

Patient characteristics and operative features. Various patient characteristics and operative features (including age, gender, preoperative biliary drainage, preoperative serum bilirubin concentration, hepatic resection, portal vein resection, pancreaticoduodenectomy, and intra-operative blood loss) were compared among the 3 groups (Table III). There were no significantly different factors among the 3 groups, except for portal vein resection. Histopathologic features of resected neoplasms, tumor size, tumor differentiation, lymph node metastases, lymphatic vessel invasion, venous invasion, perineural invasion, and T stage were examined (Table IV). There were no remarkable differences in these histopathologic features among the 3 groups, but several groups had a relatively small number of patients.

Histologic studies of cancer invasion to resected vessels. There was positive tumor invasion into the wall of the portal vein beyond the adventitia in 80% of all portal veins resected from 44 patients, includ-

Table III. Patient characteristics and surgical procedures for 161 resected patients with hilar cholangiocarcinoma

	Vascular resection			
	Portal vein alone	*Hepatic artery*	*None*	*Total*
Patients (n)	34	9	118	161
Age	64 ± 9	59 ± 9	65 ± 11	64 ± 10
Gender (male:female)	18:16	7:2	77:41	102:59
Biliary drainage	32	9	108	149
Serum bilirubin (mg/dl)	1.7 ± 1.6	2.6 ± 1.1	2.1 ± 1.4	2.1 ± 1.4
Hepatic resection	33	9	99	141
Right sided	20	2	35	57
Left sided	12	6	41	59
Central	1	1	24	25
Bile duct resection alone	1	0	19	20
Portal vein resection	34:0	7:2	0:119	41:121
Pancreatico duodenectomy	2	1	4	7
Blood loss (ml)	1,975 ± 1,474	1,726 ± 1,253	1,523 ± 1,147	1,590 ± 1,214

Table IV. Histopathologic features of resected neoplasms in 161 patients with hilar cholangiocarcinoma

	Vascular resection			
	Portal vein alone	*Hepatic artery*	*None*	*Total*
Number of patients	34	9	118	1161
Curative resection (%)	19 (56)	6 (67)	77 (65)	102 (63)
Tumor size (mm)	27 ± 10	35 ± 13	26 ± 10	26 ± 10
Tumor differentiation (well:mod:poor)*	7:21:6	1:6:2	47:49:22	55:76:30
Nodal metastasis	17	7	53	77
Lymphatic vessel invasion	32	8	104	144
Venous invasion	29	9	102	140
Perineural invasion	33	9	102	144
T_{is+1}:T_2:T_{3+4}†	0:8:24	0:1:8	7:88:25	7:97:57

*Well, moderate, and poor differentiation.
†T-staging system according to the UICC-TNM classification.

ing invasion into the adventitia in 10 patients (24%), into the media in 19 (46%), and into the intima in 4 (10%). Four of 9 patients cases (44%) had undergoing hepatic artery resection had positive tumor invasion to the adventitia. In the other 5 patients, tumor invasion did not reach the adventitia of the hepatic arterial wall, despite obvious arterial encasement in both preoperative and intraoperative findings. In 8 patients with no invasion of the portal vein, lymph node involvement was found in 5, and in 33 patients with invasion of the portal vein, nodal metastases were present in 18 (55%). There was no remarkable difference between the 2 groups.

Operative morbidity and mortality. The most serious postoperative complication encountered in this series was hyperbilirubinemia (serum T-bil >10 mg/dl) in 26 patients (16%) as shown in Table V. This serious complication resulted in lethal liver failure, accounting for 9 of 11 hospital deaths. The other common complications were pleural effusion and anastomosis breakdown of hepaticojejunostomy. None of the 41 patients with portal vein reconstruction had abnormal patency of the portal vein at any time postoperatively. Two of 9 patients after hepatic artery reconstruction developed late obstruction of reconstructed hepatic artery. Operative mortality, including hospital deaths, was 7% in the 161 resected patients. The mortality rate after the hepatic artery resection was greater than that in the non-vascular resection group ($P < .001$), but was not significantly different from that in the portal vein resection alone group, although the number were small.

Univariate and multivariate analysis of prognostic factors. Univariate survival analysis identified curability, lymph node metastases, venous invasion, perineural invasion, portal vein resection, hepatic

Table V. Operative morbidity and mortality after resection in hilar cholangiocarcinoma

	Vascular resection			
	Portal vein alone (n = 34)	*Hepatic artery* (n = 9)*	*None (n = 118)*	*Total (n = 161)*
Morbidity rate (%)	13 (38)	7 (78)	42 (36)	62 (39)
Hyperbilirubinemia	4	4	18	26
Anastomosis breakdown	3	3	14	20
Pleural effusion	7	3	14	24
Rupture of pseudoaneurysm	1	1	5	7
Mortality rate (%)	3	3	5	11(7)
Operative death	0	1	3	4
Hospital death	3	3	5	11

*Including combined resection of portal vein and hepatic artery in 7 patients.

artery resection, and hepatic resection as factors with a statistically significant prognostic influence (Table VI). Age, gender, lymphatic vessel invasion, tumor size, histologic differentiation, extended hepatectomy, and adjuvant postoperative irradiation therapy did not significantly affect prognosis after resection. Multivariate analysis suggested 4 independent prognostic factors that influenced survival after resection: curability, lymph node metastases, portal vein resection, and hepatic artery resection (Table VII). Hepatectomy was not a significant independent factor.

Survival. Survival rates in the non-vascular resection group were 63%, 39%, and 30%, 1, 3, and 5 years after resection, and were significantly better than in these who had undergone resection of the portal vein alone 50%, 19%, and 16%, and of the hepatic artery 11%, 0%, and 0%, respectively. Survival rates in the non-resection group were 15% and 0% at 1 and 2 years. There was a significant difference in survival rates between the portal vein resection alone group and the non-resection group ($P < .001$), but no significant difference between the hepatic artery resection group and the non-resection group but acknowledging the small number of patients after hepatic artery resection alone (Fig 1).

Among all patients who had undergone curative resection, survival rates of the portal vein resection alone group, the hepatic artery resection group, and the non-vascular resection group were 47%, 31%, and 25%, 17%, 0%, and 0%, and 72%, 52%, and 41% at 1, 3, 5 years postoperatively, respectively. Median survival was for 340, 213, and 1,157 days, respectively (Fig 2). Furthermore, among patients with hilar cholangiocarcinoma without lymph nodes metastases, survival rates after curative resection were 63%, 33%, and 33%, 0%, 0%, and 0% and 86%, 72%, and 57% at 1, 3, 5 years postoperatively in the portal vein resection alone, hepatic artery resection and non-vascular resection groups, respectively. Median survival in the 3 groups was for 555, 213, and 2,260 days, respectively (Fig 3). The outcome of the 33 patients with histologically positive invasion to the portal vein was not different from that of 8 patients with histologically negative invasion to the portal vein; 10% versus 25% ($P = .886$). Similarly no remarkable difference of the outcome were present in the series excluding the patients with operative or non-cancer-related deaths postoperatively; 12% versus 40% ($P = .395$) but both these latter comparisons involve few patients making the statistical comparisons not powerful. There was no obvious difference of the recurrent patterns such as local recurrence, carcinomatous peritonitis, and hepatic and extra-abdominal metastases between the groups of portal vein resection or vascular resection and no-vascular resection.

DISCUSSION

Combined vascular resection for hilar cholangiocarcinoma has been reported previously by Tsuzuki et al,[13] Sakaguchi et al,[14] and Fortner et al[15] in small series of patients. Klempnauer et al[2] first reported portal vein resection in a large series of 39 patients, and 1 patient who underwent hepatic artery resection, of 151 patients undergoing resection for hilar cholangiocarcinoma. The operative mortality rate of 17% among patients with combined vascular resection for hilar cholangiocarcinoma was high, and their aggressive approach resulted in a 5-year survival rate of 10%. Similar results, reflecting the increased risk of combined vascular resection for hilar cholangiocarcinoma, were presented in our previous report[16] and by Neuhaus et al.[6] Operative mortality in the latter 2 reports was 16% and 17%, respectively. Operative

Table VI. Univariate analysis of overall survival in patients with hilar cholangiocarcinoma*

Factor	*Survival rate (%)* 1 y	3 y	5 y	*Median survival (d)*	P *value*
Curability					
Curative (n = 59)	64	42	36	910	.0001
Non-curative (n = 102)	46	10	0	345	.0001
Nodal involvement					
Positive (n = 82)	37	13	9	305	.0001
Negative (n = 79)	79	55	42	1,185	.0001
Venous invasion					
Positive (n = 139)	59	26	21	485	.0235
Negative (n = 16)	76	61	49	1,670	.0235
Perineural invasion					
Positive (n = 140)	55	29	23	484	.0494
Negative (n = 21)	75	59	40	1,455	.0494
Portal vein resection					
Positive (n = 41)	42	16	13	325	.0006
Negative (n = 120)	63	39	30	711	.0006
Hepatic artery resection					
Positive (n = 9)	11	11	0	213	.0005
Negative (n = 152)	60	35	26	550	.0005
Hepatectomy					
Positive (n = 140)	59	35	27	606	.0282
Negative (n = 21)	39	16	11	345	.0282

*There was no significant difference of survival after surgery in age, gender, lymphatic vessel invasion, tumor size, histologic differentiation, extended hepatectomy, and adjuvant postoperative irradiation therapy.

Table VII. Multivariate analysis of overall survival in patients with hilar cholangiocarcinoma

Factor	*Relative risk*	95% CI *Lower*	*Upper*	P *value*
Curability	2.332	1.532	3.549	<.0001
Nodal involvement	2.779	1.797	4.289	<.0001
Venous invasion	1.116	0.549	2.229	.7770
Perineural invasion	1.221	0.598	2.496	.5834
Portal vein resection	1.570	1.031	2.391	.0354
Hepatic artery resection	2.293	1.052	5.000	.0369
Hepatectomy	0.803	0.465	1.389	.4333

CI, confidence interval.

mortality in combined vascular resection seemed to be affected by whether the portal vein or the hepatic artery was resected. Most reports have addressed portal vein resection such as Klempnauer et al[2] and Neuhaus et al.[6] Series that Miyazaki et al[16] and Gerhards et al[5] have reported included several patients with hepatic artery resection with 8 of 25 and 9 of 12 cases of vascular resection, respectively. Hepatic artery resection may bring about a higher operative mortality rate than portal vein resection, because hepatic artery resection has been combined with portal vein resection in most patients. Combined resection involving the portal vein and the hepatic artery may obligate longer periods of liver ischemia for vascular reconstruction, which may lead to more severe ischemic damage to the remnant liver after major hepatectomy and may result in lethal liver failure. Therefore, the portal vein resection alone group and the hepatic artery resection group should each be analyzed separately to assess how combined vascular resection can affect morbidity and mortality in operative treatment of hilar cholangiocarcinoma, and whether or not these aggressive operative approaches can bring about beneficial effects in prognosis. For this reason, our study was stratified into non-vascular resection, portal vein resection alone, and hepatic artery resection groups, to evaluate

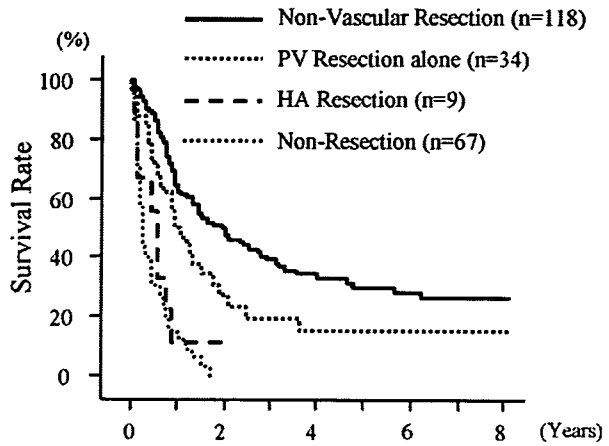

Fig 1. Survival after operative resection in all resected 161 patients. The survival rates in the non-vascular resection group and the portal vein (PV) resection alone was greater than in the non-resection group ($P < .0001$). The survival rate in the hepatic artery (HA) resection group was not different from that in the non-resection group. The survival rate in the non-vascular resection group was better than that in the portal vein (PV) resection alone ($P < .05$).

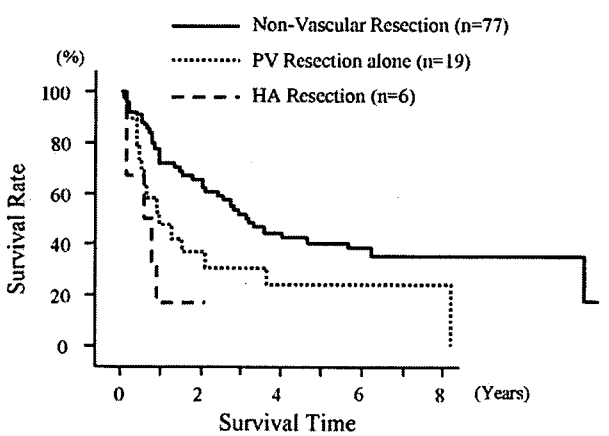

Fig 2. Survival after curative resection. Survival in the non-vascular resection group was better than in the portal vein (PV) resection group ($P < .05$).

more clearly the clinical implications of combined vascular resection for advanced hilar cholangiocarcinoma.

The 9% operative mortality rate in the portal vein resection alone group in the current study was not different significantly from the 4% rate in the non-vascular resection group. This operative mortality after combined vascular resection might be reduced by recent advances in operative technique, especially with the recent introduction of preoperative portal vein embolization and of parenchyma preserving hepatectomy.[4] Indeed, we have had no

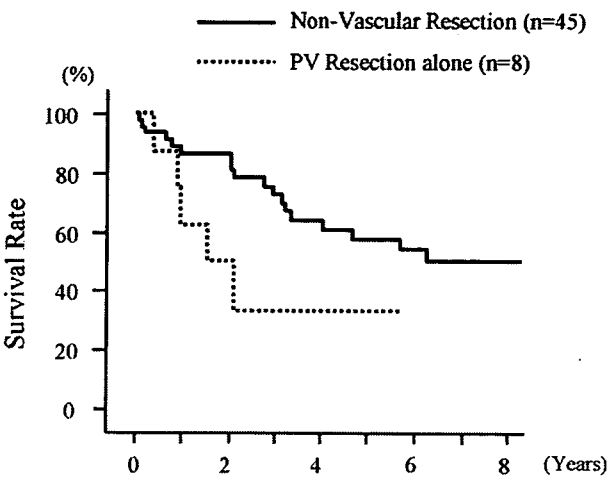

Fig 3. Survival after curative resection in hilar cholangiocarcinoma without lymph node metastases. There was no significant difference between survival rates of the non-vascular resection group and of the portal vein (PV) resection alone group.

operative deaths during the last 3 years in our institution by use of these advances; however the 33% operative mortality rate in the hepatic artery resection group was significantly greater than in the non-vascular resection group, but not significantly different from that in the portal vein resection alone group, although the numbers are small. Ebata et al[7] and Munoz et al[17] have reported a similar mortality rates of about 10%, in their portal vein resection groups of 52 patients each. There are few reports of operative mortality rates after hepatic artery resection. Madariaga et al[18] and Gerhards et al[5] have reported very high mortality rates of 5/9 and 5/9 respectively, after hepatic artery resection for hilar cholangiocarcinoma. Despite recent advances in operative techniques for hepatic artery reconstruction, as shown with results in liver transplantation several reasons might account for these high mortality rates after hepatic artery resection for hilar cholangiocarcinoma, such as a greater duration of liver ischemia due to simultaneous portal vein resection in most cases, and pre-existing liver dysfunction due to obstructive jaundice and persistent cholangitis.

The histologic features in the resected vessels were interesting, because cancer invasion into the adventitia was present in 80% of the resected portal veins and 40% of the resected hepatic arteries. In our series, combined vascular resection was carried our when cancer invasion to the vessels was diagnosed on the basis of both preoperative imaging findings and intraoperative macroscopic findings. Similar results, with no histologic invasion in 31%