Retrograde outflow isolated hepatic perfusion without laparotomy

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Background I

Isolated hepatic perfusion (IHP) has been tried by several researchers, and promising results have been obtained (Bartlett, et al. Surgery 2001, Christoforidis, et al. Eur J Surg Oncol 2002). However, this modality has not been used as a therapeutic strategy because it requires aggressive surgical intervention and can be performed only once.

Percutaneous IHP techniques using balloon catheters are simpler and facilitate repeated therapy, but resulted in far higher rates of leakage from the perfusion circuit into the systemic circulation comparison with surgical IHP techniques. (Ravikumar, et al. J Clin Oncol 1994, Savier E, et al. Arch Surg 2003)

Background II

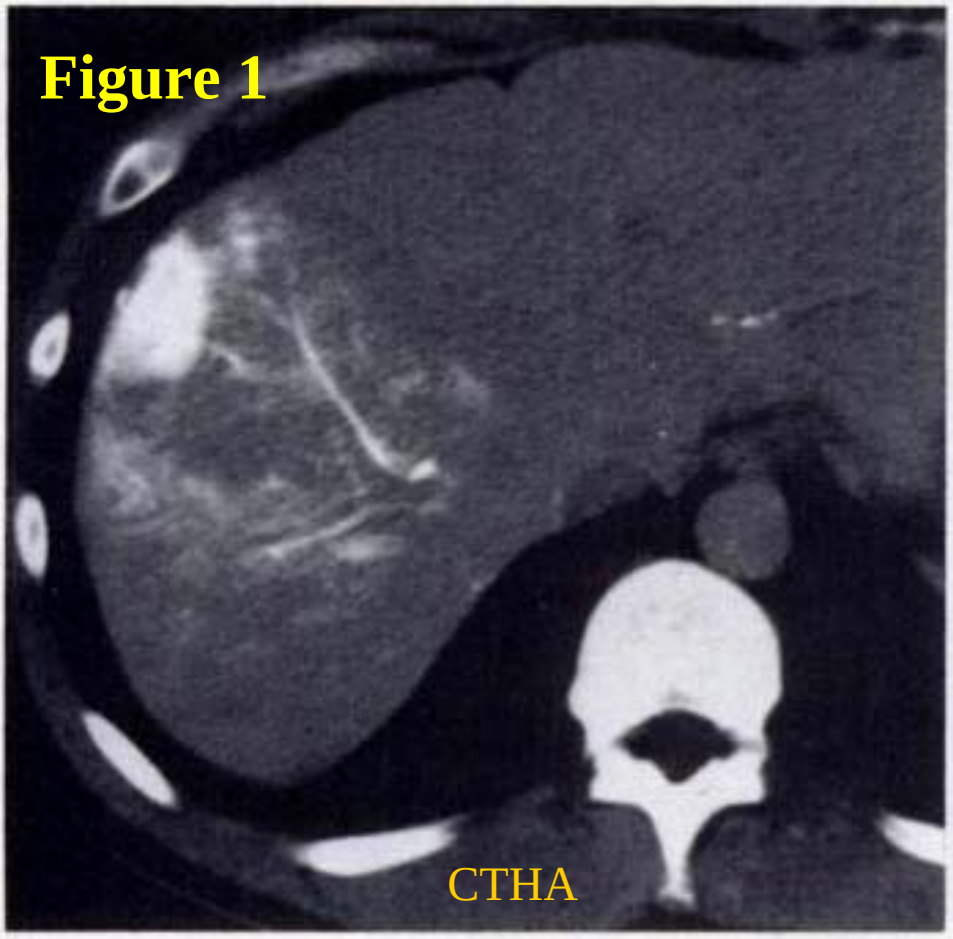
Why does percutaneous IHP lead to higher leakage rates?

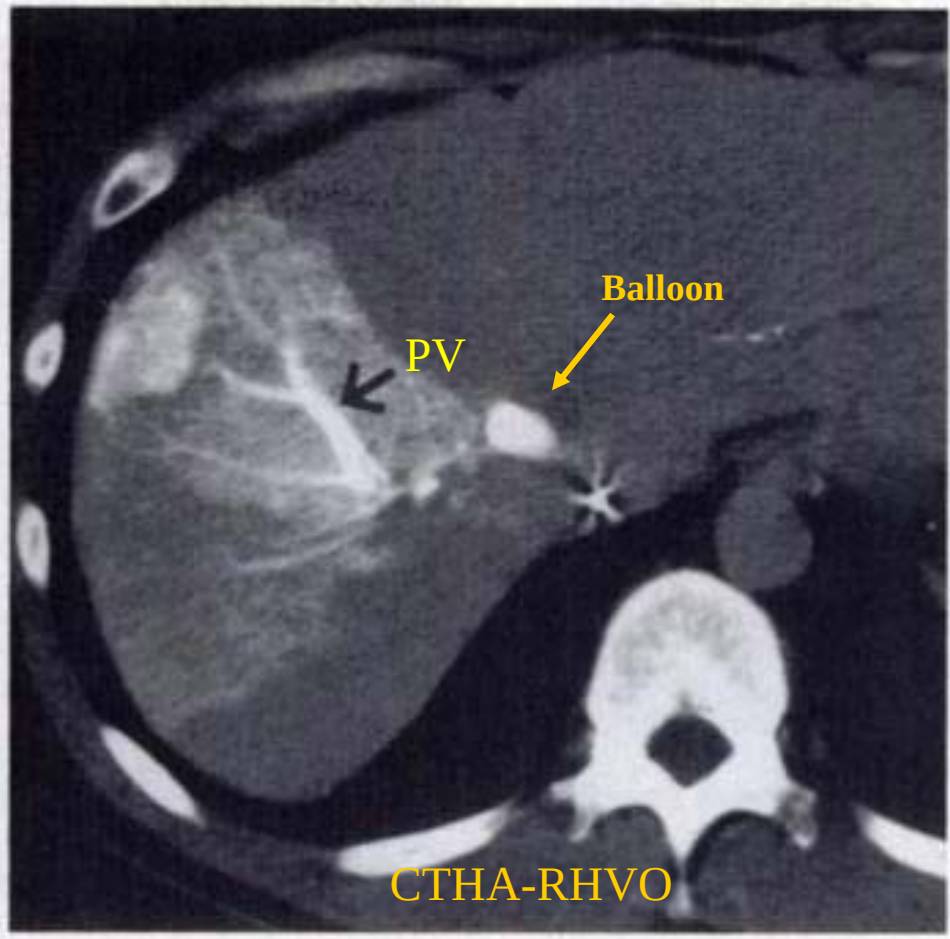
1) The shortness of the human suprahepatic vena cava.
2) Some diaphragmatic veins could be occluded during the surgical procedure by a surgical clamp but not during the percutaneous procedure by a balloon.
3) The veins around the common bile duct are not occluded by the portal occlusive balloon. (Christoforidis, et al. 2002)

Therefore, existing percutaneous orthograde IHP techniques lead to higher leakage rates.

Rationales for Retrograde outflow IHP without laparotomy

Figure 1





Murata S, et al. *Radiology* 1995, 1997

Purpose

The aim of this study was to establish a safety and repeatable percutaneous IHP with only interventional radiology techniques.

Experimental Study

Materials and Methods

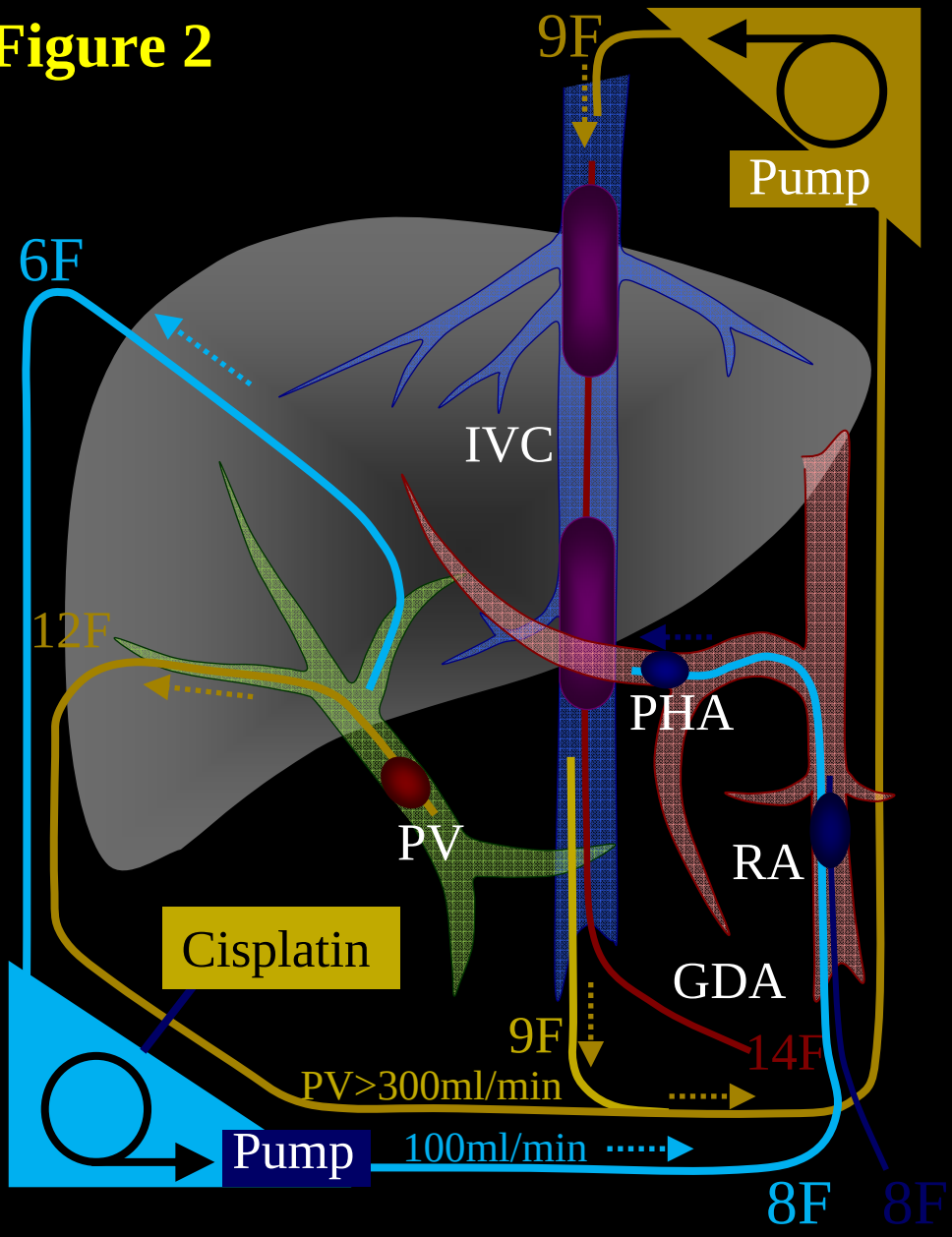
Animals: Eight male pigs weighing 39 to 44 kg (mean: 42 kg) were used.

Procedures: We performed a retrograde outflow IHP with a double balloon blocking outflow into IVC and allowing outflow via the portal vein. Blood with cisplatin (2.5 mg/kg) in the extracorporeal circuit was circulated in the liver with rotary pumps under isolation with balloon catheters.

Examination items:

1) Hepatic angiographic examinations during perfusion
2) Histologic examinations after perfusion
3) Pharmacokinetics; the maximum platinum concentration (C-max), concentration-time curve (AUC)

Figure 2



Isolated Liver Perfusion

Results I

Hepatic angiographic examinations during perfusion

Hepatic angiographic examinations during perfusion

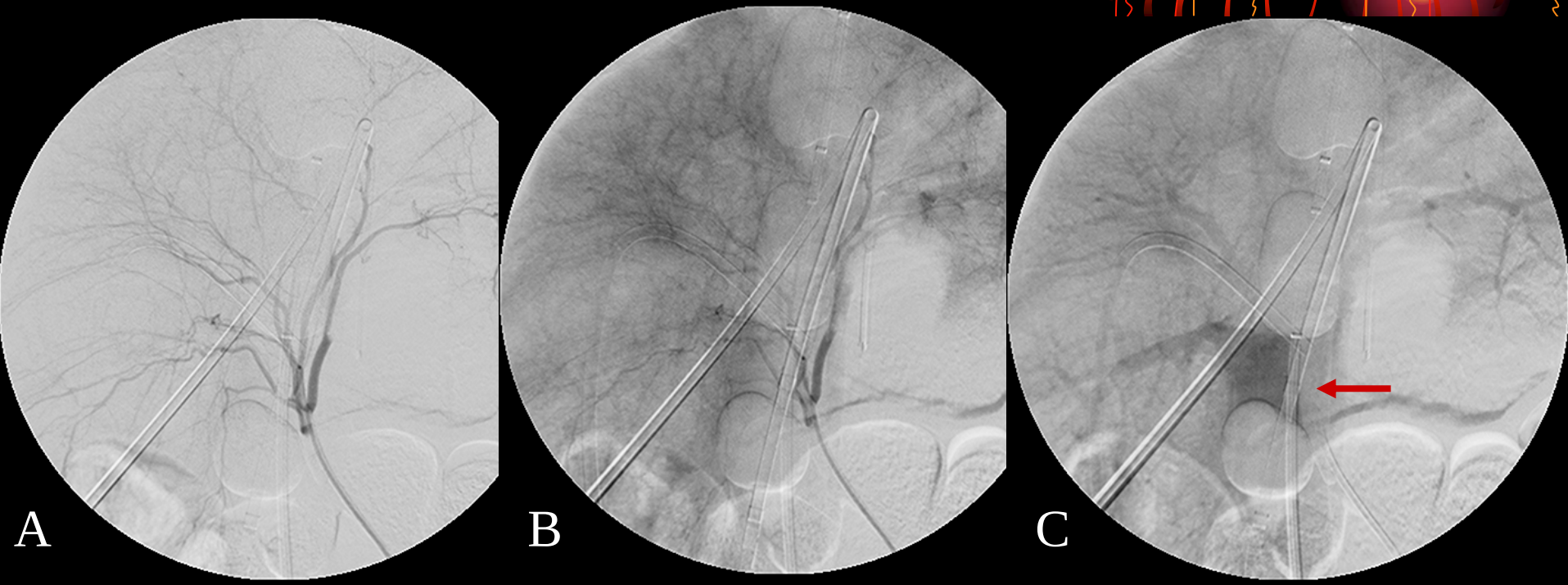
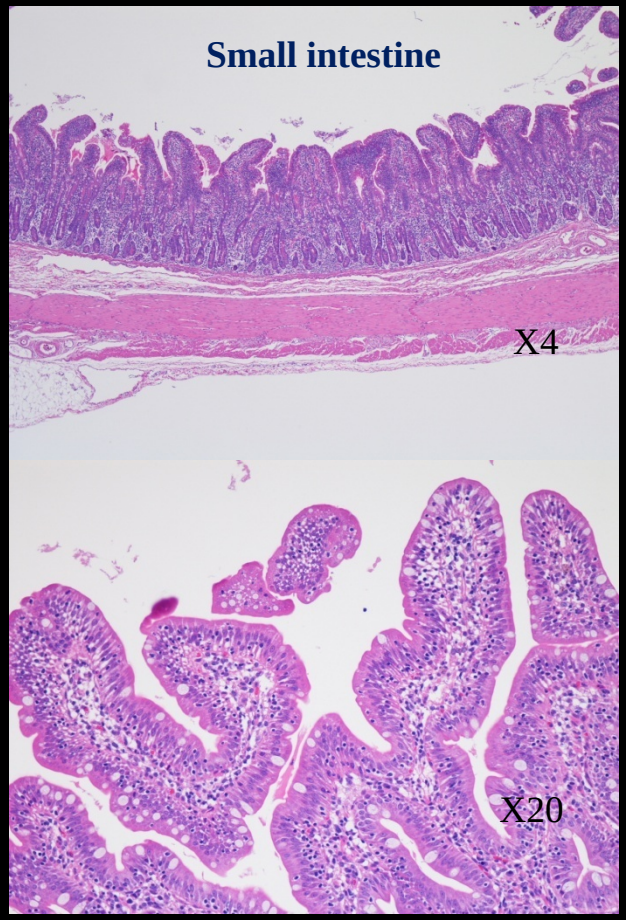


Figure 3 A; arterial phase, B; delayed arterial phase, C; portal phase
Isolated hepatic angiography confirm that contrast media flow into the liver, and flow into the intrahepatic portal vein (PV). The contrast opacification of the main PV increases with time (arrow), confirming that the PV acts as an outflow tract. No collateral vessels to the surrounding organs are opacified during isolated hepatic arteriography.

Results II

Histologic examinations after perfusion



There were not observed structural disorder, dilatation of the sinusoids, and thrombus in the vessels in the liver. Duodenum, small intestine, and colon had no edematous changes and ischemic changes.

Results III

Pharmacokinetics; C-max & AUC

Table 1. The *C*max and AUC of cisplatin in the hepatic and systemic circulation

	Liver circulation			Systemic circulation			Liver-to-systemic exposure ratio		
	*C*max	AUC	Mean	*C*max	AUC	Mean	*C*max	AUC	Mean
Pig 1	95.5	1500.7	50.0	1.1	13.6	0.5	85.3	110.5	110.5
Pig 2	78.5	1443.4	48.1	3.3	67.4	2.2	23.8	21.4	21.4
Pig 3	63.9	999.5	33.3	1.2	19.7	0.7	55.1	50.7	50.7
Pig 4	112.8	1802.1	60.1	2.0	37.7	1.3	57.3	47.8	47.8
Pig 5	51.8	1184.3	39.5	0.5	9.3	0.3	101.6	128.0	128.0
Pig 6	103.3	1305.2	43.5	3.3	81.9	2.7	30.9	15.9	15.9
Pig 7	92.6	863.5	28.8	2.0	44.3	1.5	47.0	19.5	19.5
Pig 8	105.2	1317.5	43.9	3.4	60.4	2.0	31.4	21.8	21.8
Mean	87.9	1302.0	43.4	2.1	41.8	1.4	41.9	31.1	31.0
95%CI	70.0–105.8	1055.7–1548.3	35.2–51.6	1.2–3.0	19.5–64.1	0.7–2.1	31.1–77.0	15.3–88.6	15.3–88.6

The *C*max is represent in mg/L, and the AUC of 0–30min is indicated in mg min/L

Pharmacokinetics; C-max & AUC

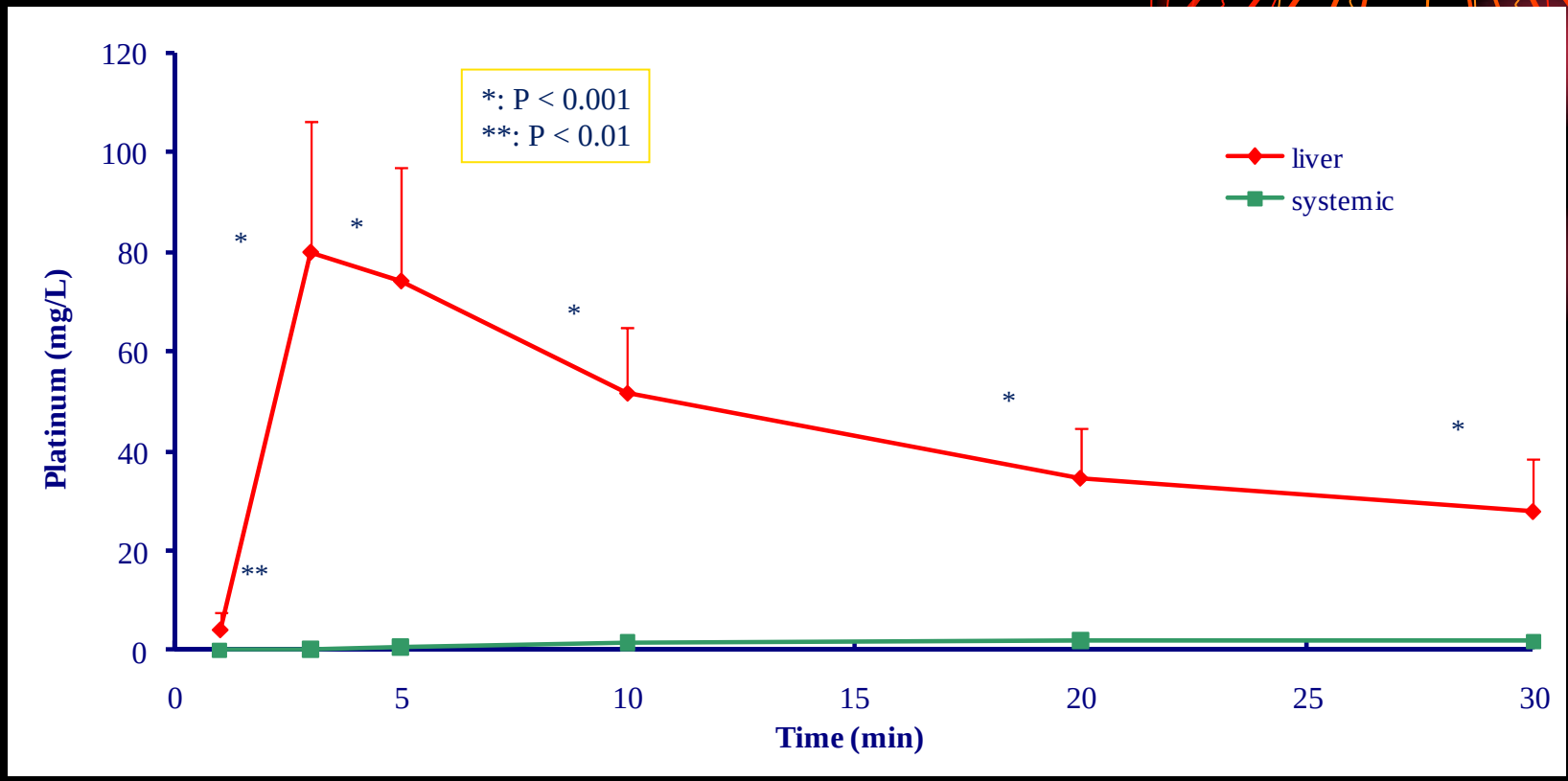


Figure 6. Serum plasma platinum concentrations during retrograde-outflow isolated hepatic perfusion. All of the platinum concentrations in the hepatic circulation were significantly higher ($P < 0.01$, unpaired *t*-test) than those in the systemic circulation.

Discussion I

I. Advantages of our retrograde IHP technique

Problems of a orthograde percutaneous IHP
(1) The shortness of the human suprahepatic vena cava.
(2) Some diaphragmatic veins could not be occluded during the percutaneous procedure by a balloon.
(3) The veins around the common bile duct are not occluded by the portal occlusive balloon.

Our retrograde IHP technique resolves the problems of (1) and (2). However, (3) has not been resolved yet.

Discussion II

II. Our retrograde outflow IHP is alternative to surgical IHP?

Pharmacokinetics

The pharmacokinetics results of this study were superior to those of other published orthograde non-surgical IHP in clinical. However, our results were a little inferior to those of other published orthograde surgical IHP.

Advantage of surgical IHP compared to our retrograde IHP

The veins around the common bile duct are occluded by surgical clump, but not by the portal occlusive balloon.

Advantage of our retrograde IHP compared to surgical IHP

Our retrograde IHP may be less invasive (without laparotomy)
may be repeatable.
may be less costly.

Limitation

Retrograde-outflow IHP system cannot be performed in the case of portal vein trunk obstruction due to tumour invasion or thrombus.

Conclusion

Repeatable percutaneous retrograde IHP therapy with only interventional radiology techniques may be realize, safety and useful for management of liver tumors.

To be continued……

Retrograde outflow IHP in clinical

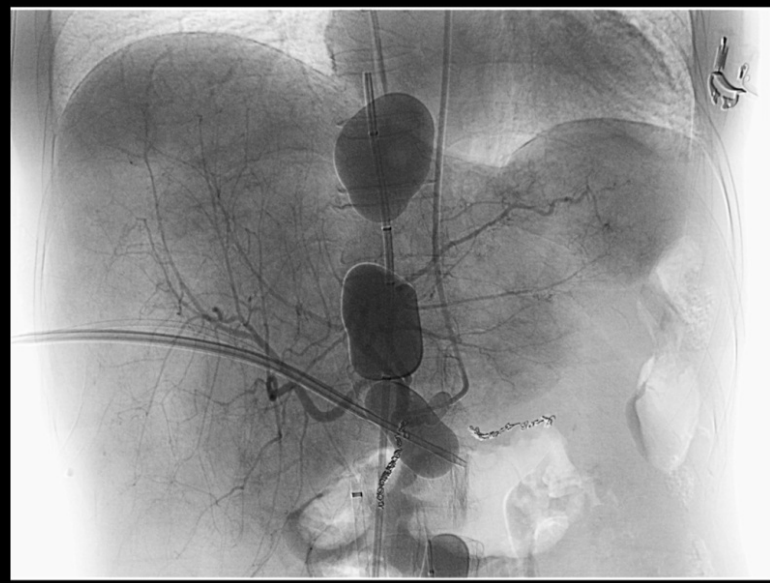
Indication: cholangiocarcinoma, hepatocellular carcinoma, liver metastasis.

Methods:

(1) Percutaneous retrograde-outflow IHP for 30 min.

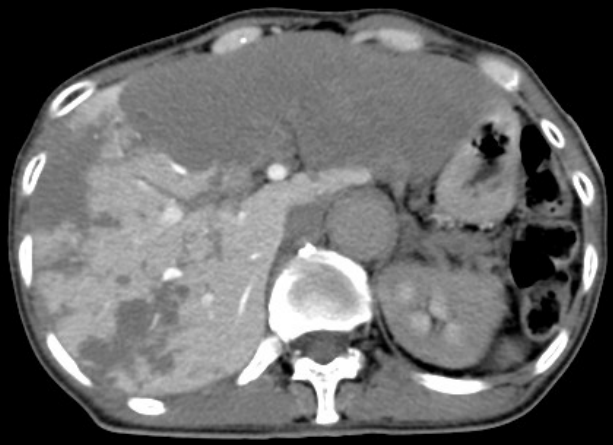
(2) Perfusion with isotonic sodium chloride solution for 10 min to remove drugs from the liver.

(3) Total isolation time should be within 45 min.



Case 1: Advanced cholangiocarcinoma

60- year- old, woman



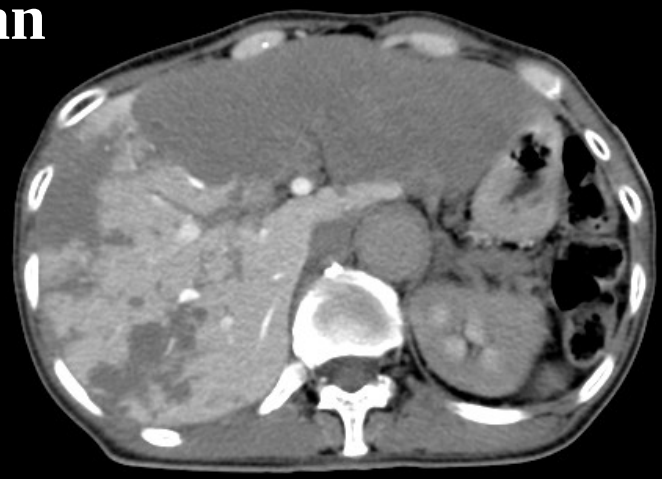
CT-AP

Positioning of a portal occlusive balloon

Case 1: Advanced cholangiocarcinoma

60- year- old, woman

Liver is occupied by multiple tumors.
Retrograde IHP is performed.



Before IHP

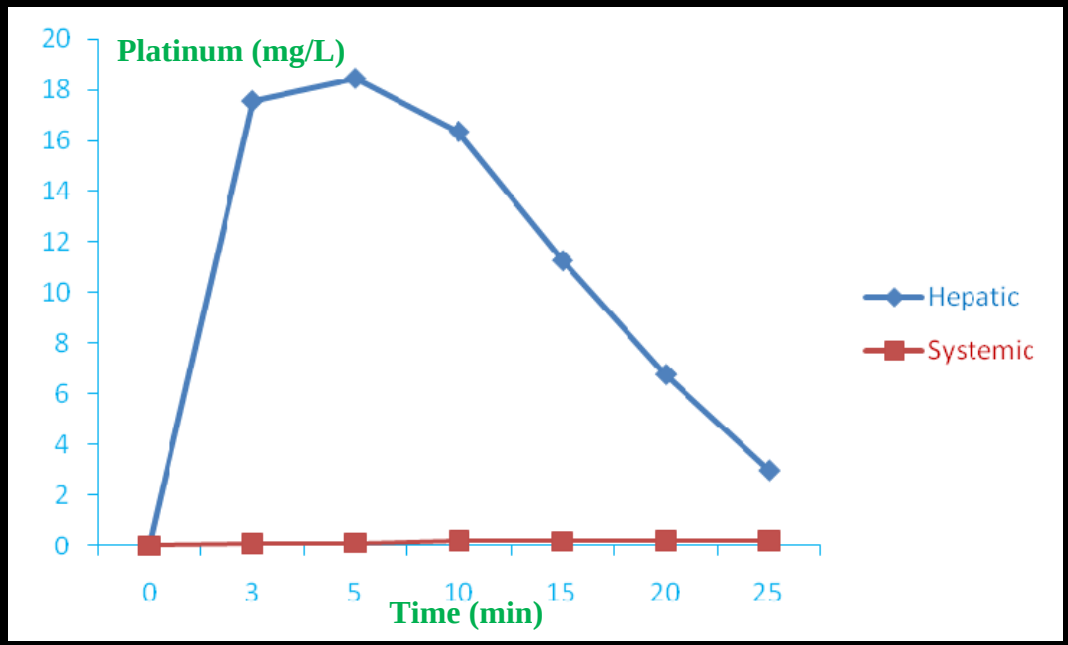
3 weeks after IHP

Toxicity: comparison of the IHP toxicities with previously reported data

	Surgical	Combination	Percutaneous	Percutaneous (present study)
Ascites	75- 100%	75%	17%	none
Pleural effusion	19- 100%	100%	100%	none
MOF	5- 13%	0-?	0%	none
VOD	8.6- 44%	10- 18%	0%	none
(Vascular occlusive disease)				
HA thrombosis	2- 9%	25%	0%	none
Reoperation	10- 73%	0- 4%	0%	none
Bleeding	8.6- 45%	0%	0%	none
Mortality	4- 7%	3%	0%	none
(VOD or Hepatic failure)				
Leukopenia	10- 71% (Grade 3-4)	13% (Grade3-4)	67% (Grade3-4)	none
Bilirubin	18- 47% (Grade3-4)	17% (Grade3-4)	-	none

Contrary to other IHP techniques, there was no major complication occurred by our retrograde IHP.

Pharmacokinetics



Regimen for CCC
Gemzar + CDDP (40 mg/m2)
in a stepwise fashion.

C-max ratio = 70.3
AUC ratio = 40.3

Discussion

The Cmax and AUC of Drugs in the Hepatic and Systemic Circulation: Comparison of the IHP Values with Previously Reported Data

Stage	Technique	Method	Drugs	Number	C_{max} (mg/L) LC/SC Ratio	AUC (mg min/L) LC/SC Ratio	Leakage Rate (mean, %)	Reference
pig	**Percutaneous**	Retrograde	Cisplatin	8	**41.9**	**31.1**	-	Present study
pig	Combination	Orthograde	Melphalan	2	33	20.4	-	[26]
			MMC	2	38	27.9	-	
			TNF	3	>38	43.3	-	
pig	Surgical	Orthograde	Melphalan	10	-	-	8	[27]
human	Combination	Orthograde	Melphalan	8	-	-	56	[24]
	Combination	Retrograde	Melphalan	10	-	-	35	
human	Surgical	Orthograde	Melphalan	4	16.7–25.0	-	-	[19]
	Percutaneous	Orthograde	Melphalan	6	<10	-	-	
human	Surgical	Orthograde	Melphalan	20	-	52.0	3	[29]
human	**Percutaneous**	Retrograde	Cisplatin	2	**70.3**	**40.3**	-	Present study

Note.—The combination therapy comprised laparotomy and percutaneous techniques.

Abbreviations.—LC = liver circulation; SC = systemic circulation;

Discussion

In clinical the pharmacokinetic data demonstrated that retrograde-outflow IHP is not inferior to surgical IHP and that it is superior to other published nonsurgical IHP techniques or a combination of laparotomy and percutaneous IHP.

Why

Because it is much easier to make a retrograde-outflow IHP system in clinical. It works very well during perfusion.

With our data high leakage in the percutaneous IHP is mainly caused by incomplete occlusion of the IVC included diaphragmatic veins.

Conclusion

The full potential of percutaneous IHP therapy will be realized if the retrograde-outflow percutaneous IHP method is used.

Thank you for your time and attention.