Negative-balance isolated pelvis perfusion

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Outline

- About Negative-balance Isolated Pelvic Perfusion (NIPP)
- NIPP for rectal cancers

Background

In 1958, Creech et al. established the theory of Isolated regional perfusion chemotherapy. (Annals of Surgery)

In 1959, Austin et al reported the isolated perfusion of the pelvis (IPP) for inoperable malignancy in the pelvic cavity. (New England Journal of Medicine)

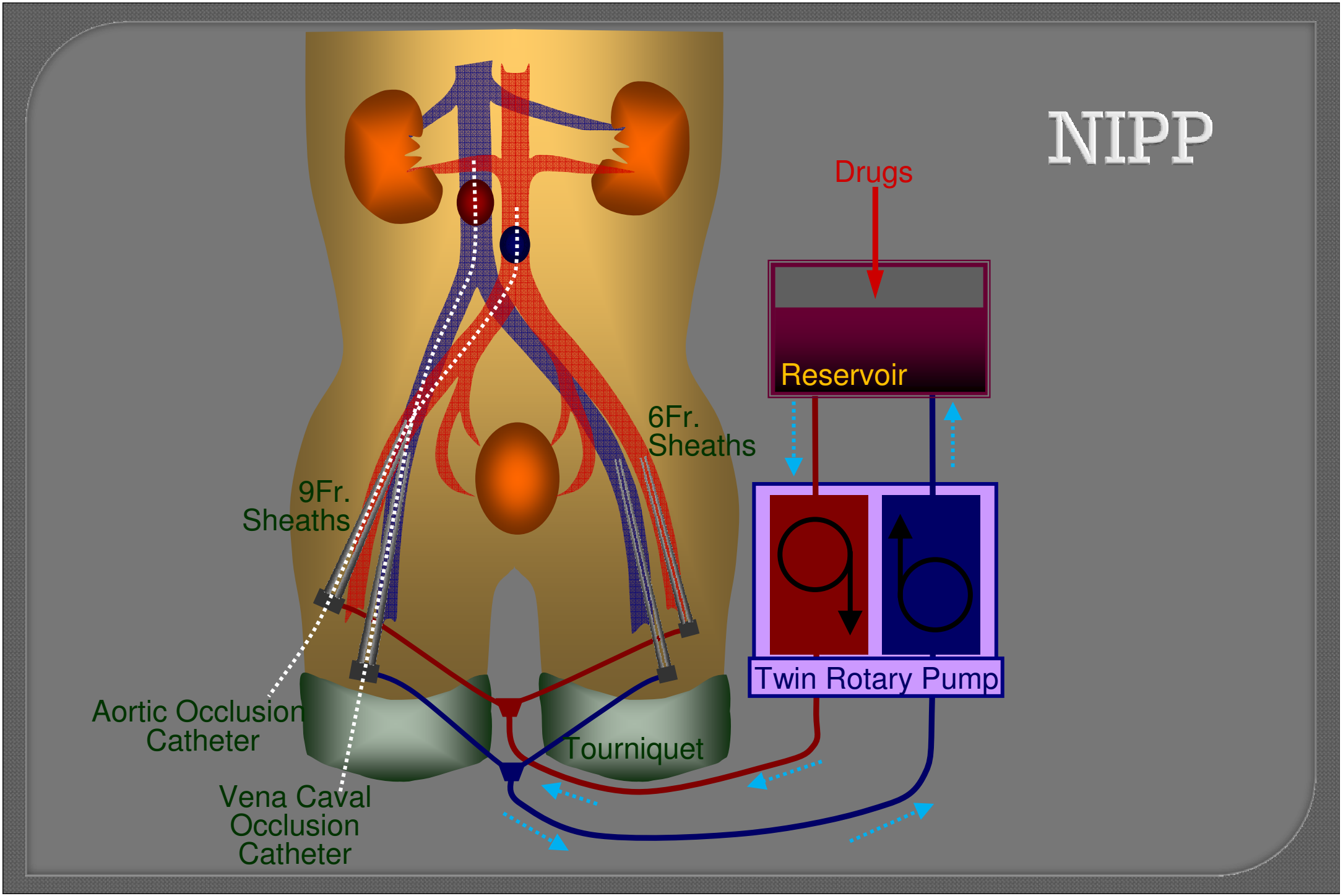
Two problems in IPP

1. Leakage: because of the collateral circulation, anti cancer drug can leak to systemic perfusion.
2. No retrieve of anti cancer drug

Therefore they cannot use anti cancer drug more than normal limit.

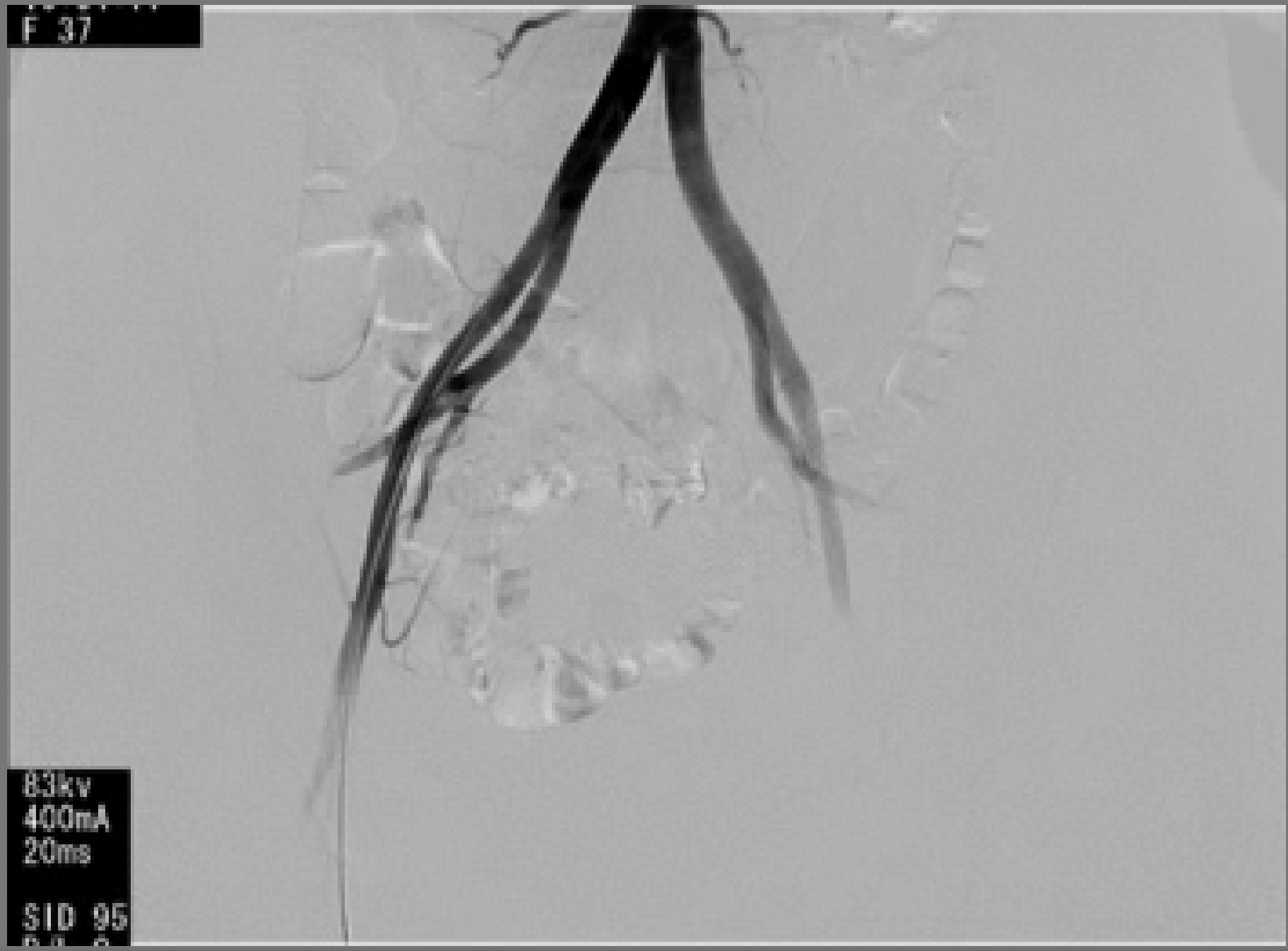
Introduction

- To avoid the leakage, we establish the new technique, **N**egative-balance **I**solated **P**elvic **P**erfusion (**NIPP**).
- To retrieve anticancer drug, we use the hemodyalsis just after the NIPP for pelvic circulation.


NIPP
Drugs
Reservoir
6Fr.
Sheaths
9Fr.
Sheaths
Twin Rotary Pump
Aortic Occlusion
Catheter
Tourniquet
Vena Caval
Occlusion
Catheter

Negative-balance Isolated Pelvic Perfusion (NIPP)

- During the NIPP treatment, the pelvic circulation is isolated from systemic circulation due to the occlusion of Aorta and inferior vena cava. Artificial drainage of blood from pelvic circulation is made by the differentiation between inflow and out flow. This artificial drainage reduces the leakage of the anti cancer drugs from pelvic cavity and keeps high concentration of the drugs in the pelvic cavity.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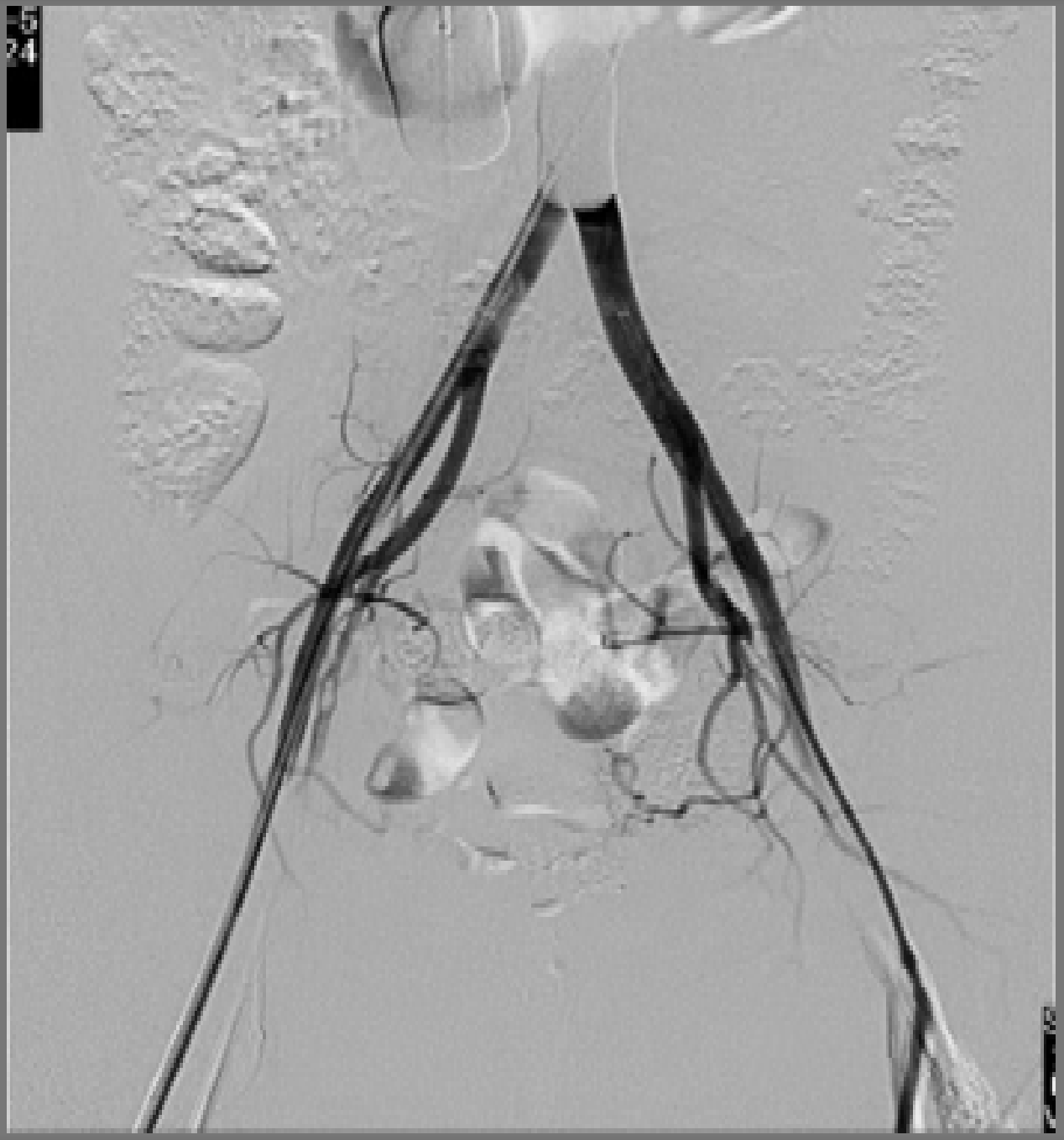
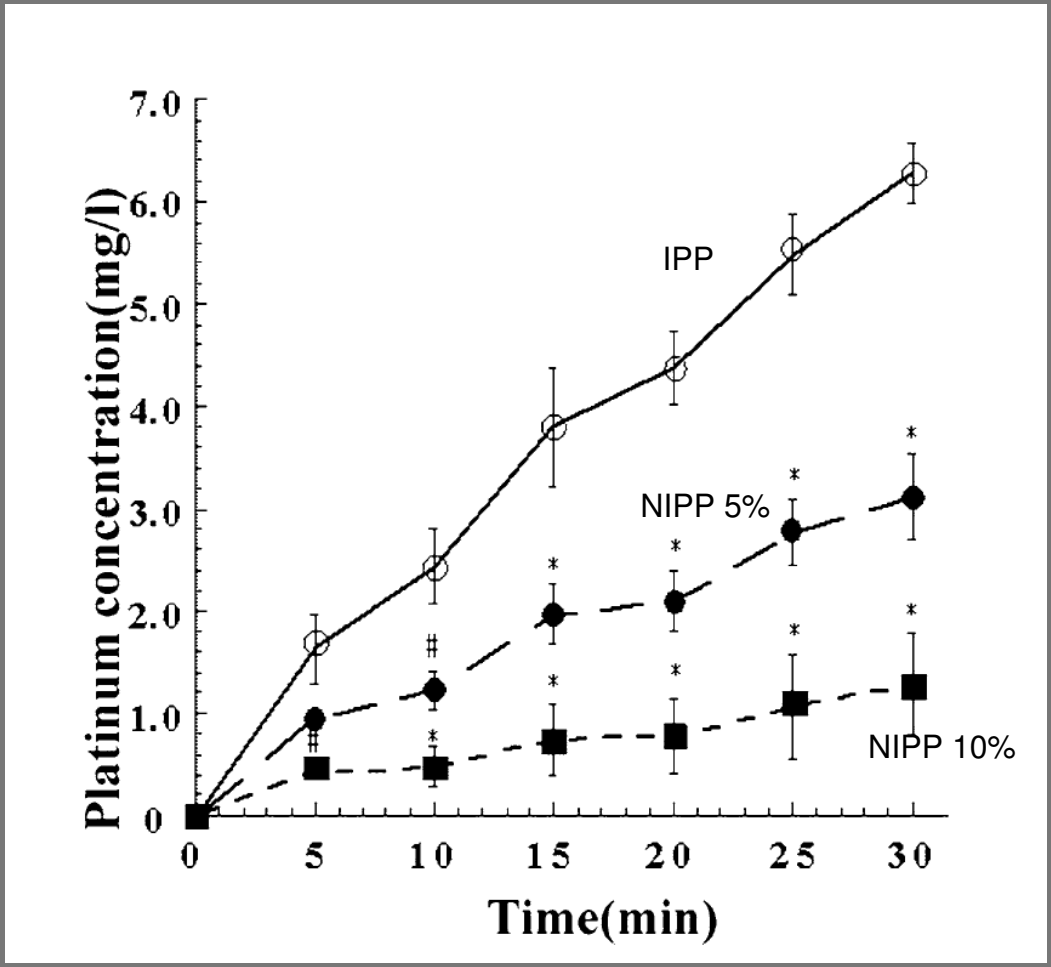


NIPP

CDDP leakage to systemic circuration



NIPP reduces the leakage of CDDP.

$$\text{Percentage} = \frac{\text{Outflow} - \text{Inflow}}{\text{Inflow}}$$

Purpose

- We develop NIPP from the experimental work to the clinical study. Our primary goal was to establish a safe regimen for high-dose regional chemotherapy.

- The purpose of this study is to assess the safety and feasibility of NIPP for recurrent rectal cancer patients prospectively.

Materials and Methods

- 30 consecutive cases of recurrent rectal cancers treated with NIPP
- Except the renal failure patients
- We performed NIPP with general anesthesia and just after the NIPP hemodialysis was done.

NIPP methods

- Artificial drainage during the procedure was 25ml/min.
- 30min treatment with NIPP.
- Cisplatinum(CDDP) was used for the treatment and every 1/3 of drug was injected in every 10 minutes.
- Total amount of drug was increased stepwise manner from 150mg/m^2 to 200mg/m^2 with 10mg/m^2

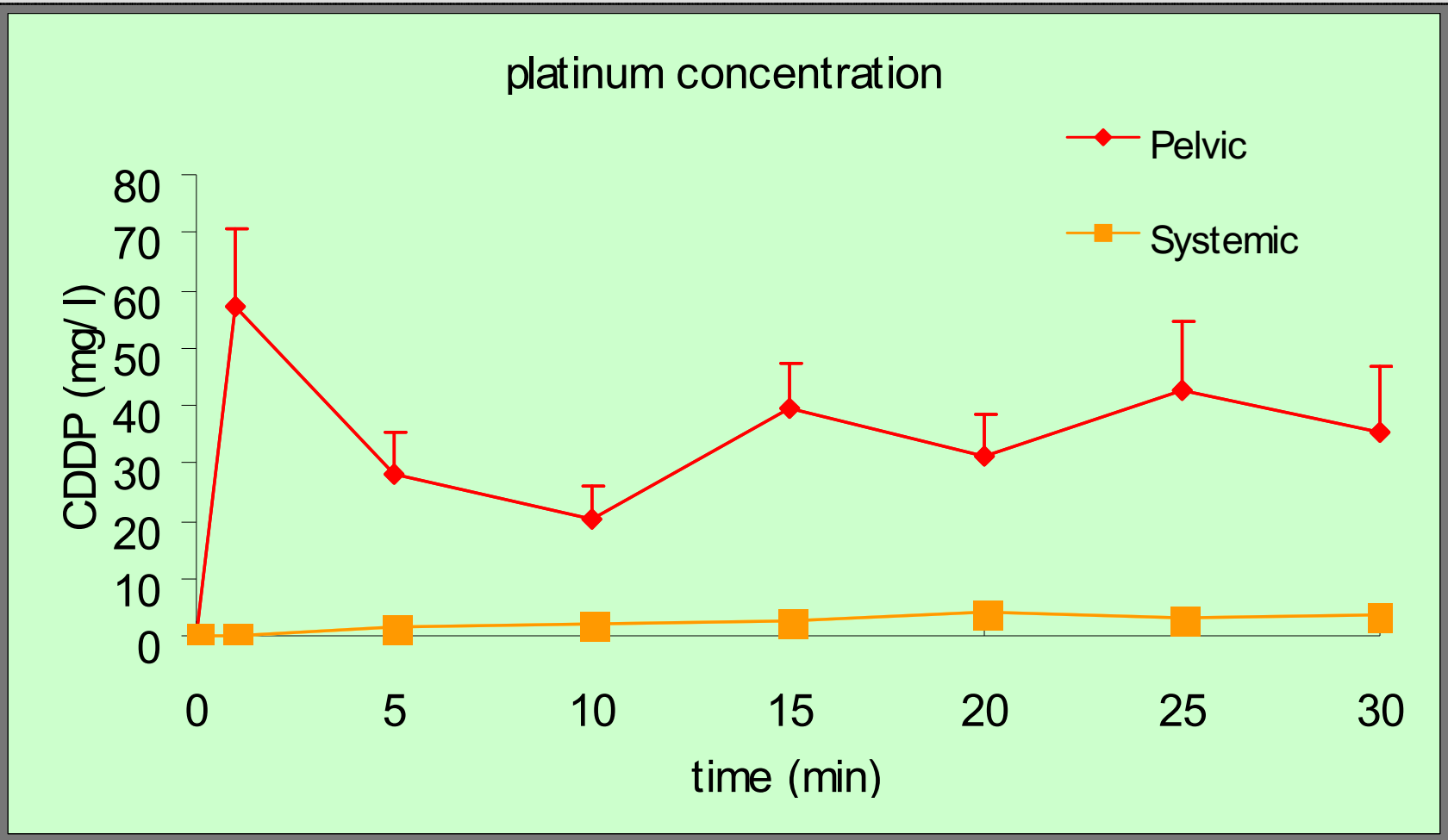
Assessment

- Concentration of CDDP during NIPP in systemic and pelvic circulation.
- Toxicity of CDDP
- Pain control, Performance Status
- Effects of the anti cancer treatment

Patient character

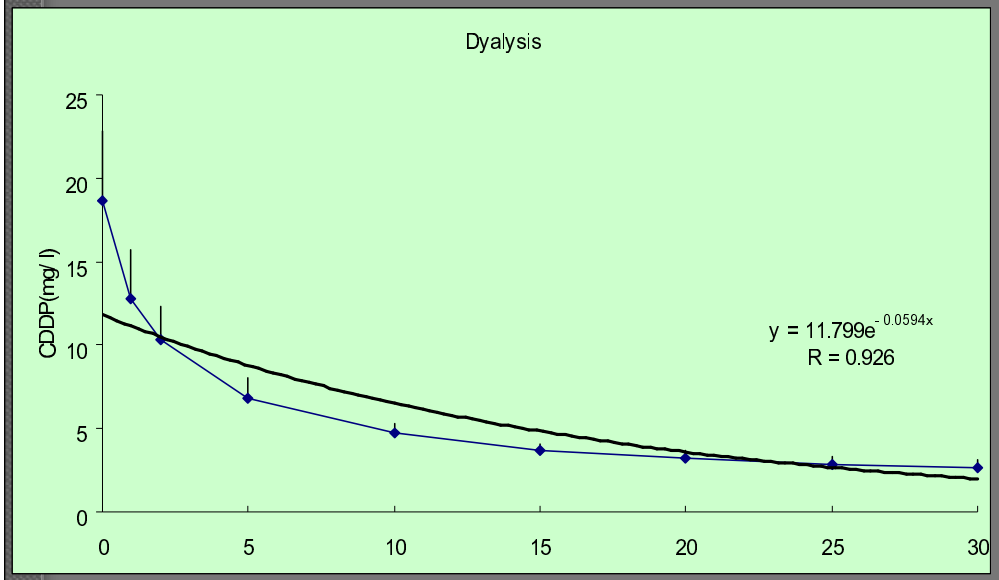
		First operation		Radiation		Dissemination	
	Overall (n=30)	Curative (n=21)	Palliative (n=9)	Received (n=22)	non-received (n=8)	Positive (n=20)	non (n=10)
Demography							
Age	56 (44-76)	57 (44-73)	53 (44-76)	55 (44-63)	59 (44-76)	55 (44-76)	59 (52-73)
M/F	19 /11	10 /11	9 /0	15 /7	4 /4	15 /5	4 /6
		P=0.011					
Performance status							
0/1/2/3	0/8/17/5	0/5/11/5	0/3/6/0	0/5/13/4	0/3/4/1	0/4/14/2	0/4/3/3
Direct invasion	(n=22)	(n=15)	(n=7)	(n=17)	(n=5)	(n=17)	(n=5)
bladder or ureter	20	13	7	16	4	17	3
bone	7	3	4	5	1	5	2
muscle	6	4	2	3	3	4	2
uterus	5	5	0	4	1	4	1
Dissemination	n=21	n=11	n=9	n=17	n=3	n=20	n=0
		P=0.013					
Metastases	(n=21)	(n=15)	(n=6)	(n=17)	(n=4)	(n=15)	(n=6)
liver	10	7	3	7	3	6	4
lung	10	7	3	9	1	8	2
paraaortic LN	15	10	5	12	3	12	3
bone	1	1	0	0	1	0	1
others	2	2	0	1	1	1	1
Dissemination & Metastases	n=15	n=9	n=6	n=13	n=2	n=15	n=0
Fistula	(n=7)	(n=6)	(n=1)	(n=7)	(n=0)	(n=5)	(n=2)
enterovesical	3	2	1	3	0	2	1
enterovaginal	4	4	0	4	0	3	1
Hydronephrosis	(n=20)	(n=13)	(n=7)	(n=16)	(n=4)	(n=16)	(n=4)
bilateral	8	4	4	7	1	7	1
unilateral	12	9	3	9	3	9	3
Nephrostomy	n=5	n=3	n=2	n=5	n=0	n=5	n=0
Previous therapies							
chemotherapy	30	21	9	22	8	20	10
radiation	22	15	7	22	0	17	5

CDDP concentration during NIPP



During NIPP, CDDP concentration in pelvic circulation was significantly higher than in systemic circulation ($P<0.001$).

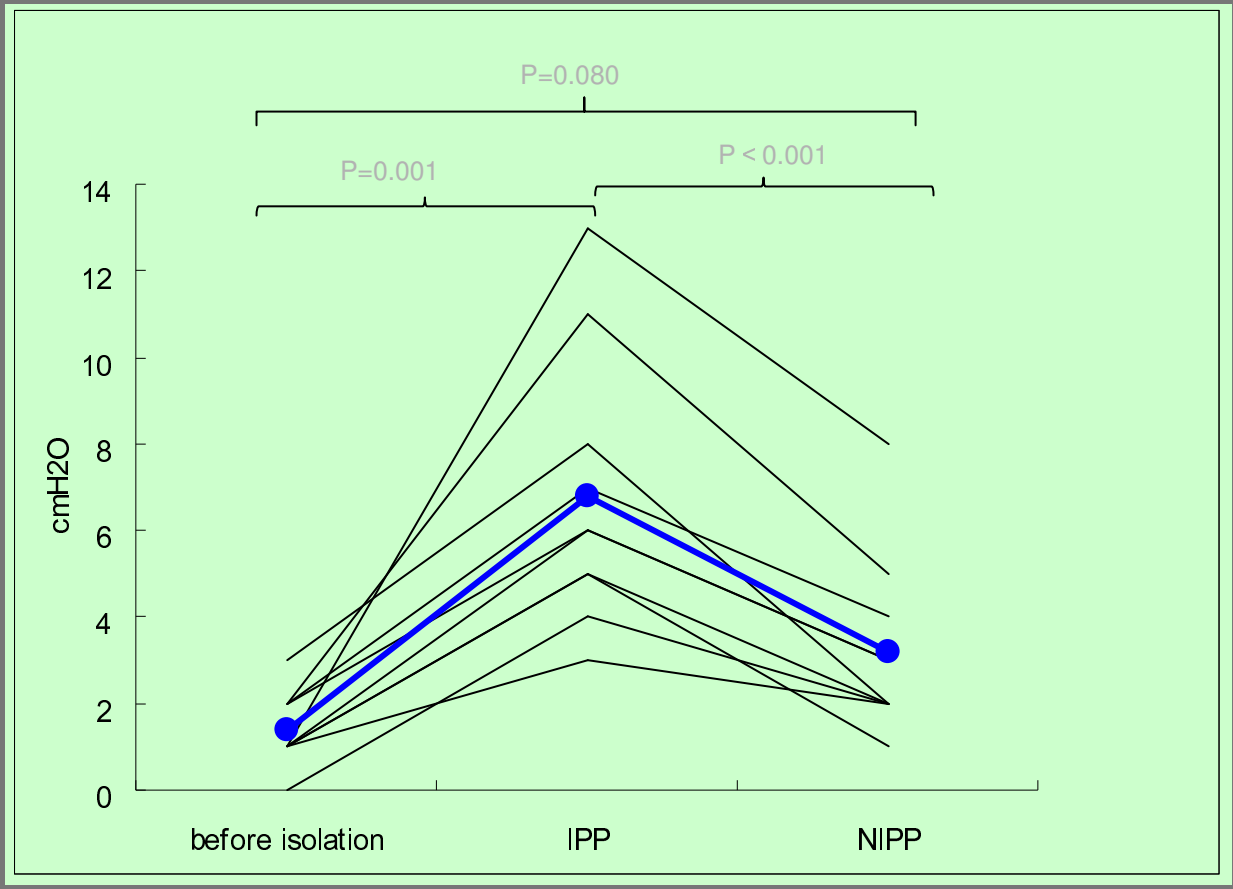
NIPP後　透析中 platinum濃度



After NIPP (min)	0	1	2	5	10	15	20	25	30
Average (mg/L)	18.69	12.83	10.32	6.78	4.74	3.69	3.25	2.88	2.65
SD	4.11	2.85	2.01	1.27	0.61	0.42	0.43	0.43	0.49

血液透析により骨盤内platinum濃度は減少し、血液透析でCDDPが濾過された。
近似曲線から半減期は約11分であった。
20分以降、platinum濃度はほぼplateauに達した。

Venous pressure gradient



CVPとpelvic venous pressureの差 = Venous pressure gradient はNIPP前で最も低く(1.4±0.8cmH_2O)、IPP状態では上昇(6.8±3.1)、NIPPで(3.2±2.0)となり、骨盤外へと流出する静脈圧は減少する

Toxicity

	Neuropathy			Creatinine			
	II	III	P	I	II	III	P
Cisplatin dose (mg/m2)							
150	0	0		1	0	0	
160	0	0		1	0	0	
170	0	0	0.033	1	0	0	0.574
180	0	0		1	0	0	
190	0	0		1	1	0	
200	2	0		0	1	0	

Spearman's rank correlation coefficient

Significant relation between CDDP dose and Neuropathy was seen.

There is no toxicity more than grade III in the other scale.

		Grade			
Toxicity	**(n=30)**	I	II	III	IV
Gastrointestinal					
Nausea/Vomiting	23 (76.7%)	12	11	0	0
Anorexia	25 (83.3%)	22	3	0	0
Vascular					
Dissection	0	0	0	0	0
Thrombus	0	0	0	0	0
Others					
Leukopenia	5 (16.7%)	2	3	0	0
Tinnitus	0	0	0	0	0
Neuropathy	2 (6.7%)	-	2	0	0
Fever	9 (30.0%)	7	2	0	0
Creatinine	7 (23.3%)	5	2	0	0
Renal failure	0	-	-	0	0

All data was defined by National Cancer Institute-Common Toxicity Criteria (NCI-CTC Version 2.0).

Pain control & Performance Status

	PD	NC	PR	CR	P
Cisplatin dose (mg/m_2)					
150	0	0	2	3	
160	0	0	4	1	
170	0	0	3	2	0.181
180	0	0	5	0	
190	0	1	4	0	
200	0	0	3	2	

Performance status	**Before NIPP**	**After NIPP**	**P****
0/1/2/3	**0/4/15/11**	**3/17/8/2**	**<0.001**

*,Spearman's rank correlation coefficient

**, Wilcoxon signed rank test

Pain control was obtained even in the minimum dosage.
Performance Status was improved after NIPP.

NIPP前治療、播種の有無による腫瘍縮小効果

	Pelvis						Extra-pelvis	
	PD	SD	PR	CR	P		PD	SD
First operation								
Curative (n=21)	0	14	5	2	0.03*	(n=15)	8	7
Palliative (n=9)	2	7	0	0		(n=6)	5	1
Pre-radiation								
Rad (n=22)	2	18	2	0	0.003*	(n=17)	11	6
non-Rad (n=8)	0	3	3	2		(n=4)	2	2
Peritoneal dissemination (PD)								
PD (n=20)	2	16	2	0	0.015*	(n=15)	11	4
non-PD (n=10)	0	5	3	2		(n=6)	2	4
Cisplatin dose (mg/m2)								
150	0	5	0	0	0.088**	(n=4)	4	0
160	1	3	1	0		(n=5)	2	3
170	0	3	2	0		(n=5)	1	4
180	1	4	0	0		(n=4)	3	1
190	0	4	1	0		(n=2)	2	0
200	0	2	1	2		(n=1)	1	0

*, Wilcoxon signed rank test

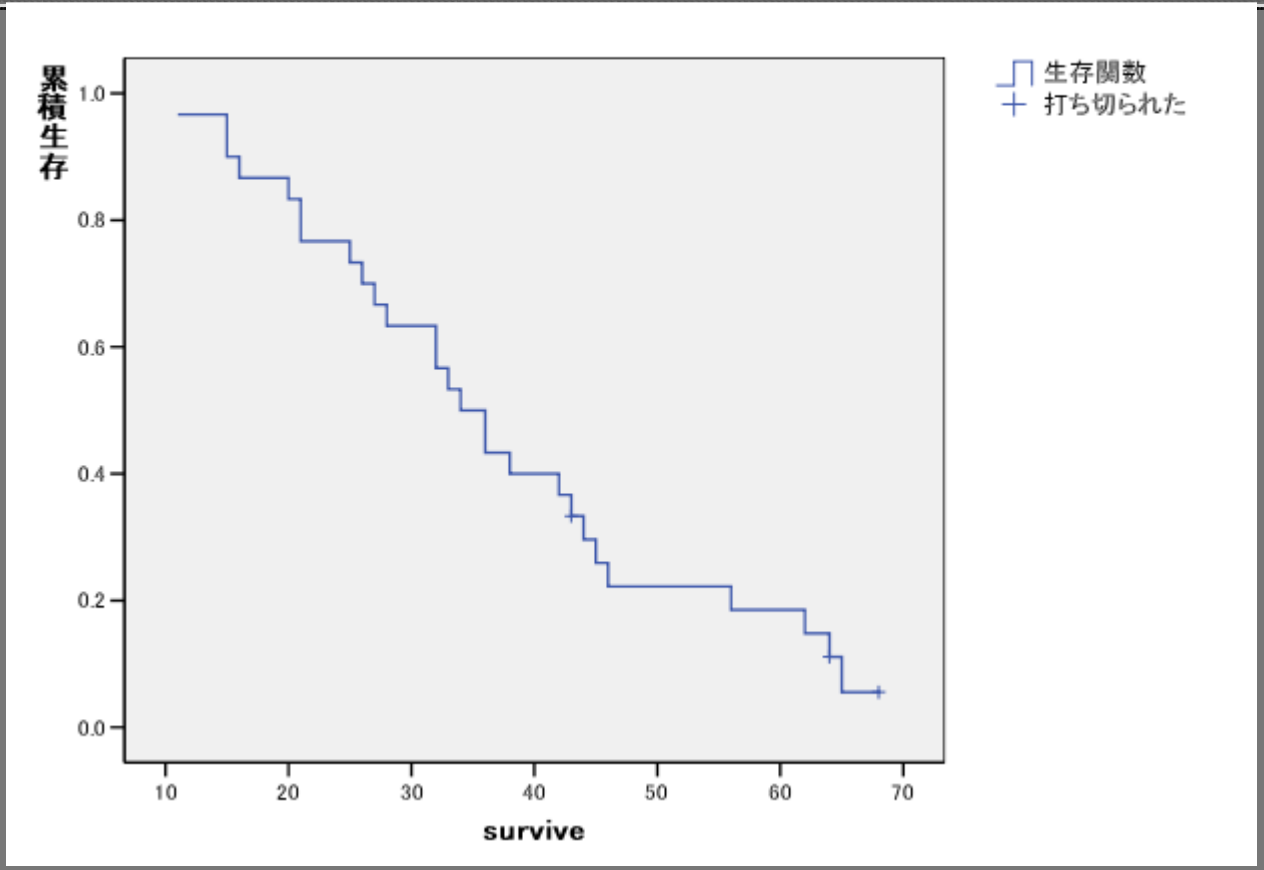
**, Spearman's rank correlation coefficient

NIPP前の手術がcurative群で、有意に治療効果が良好であった。

NIPP前の放射線治療歴がない群で、有意に治療効果が良好であった

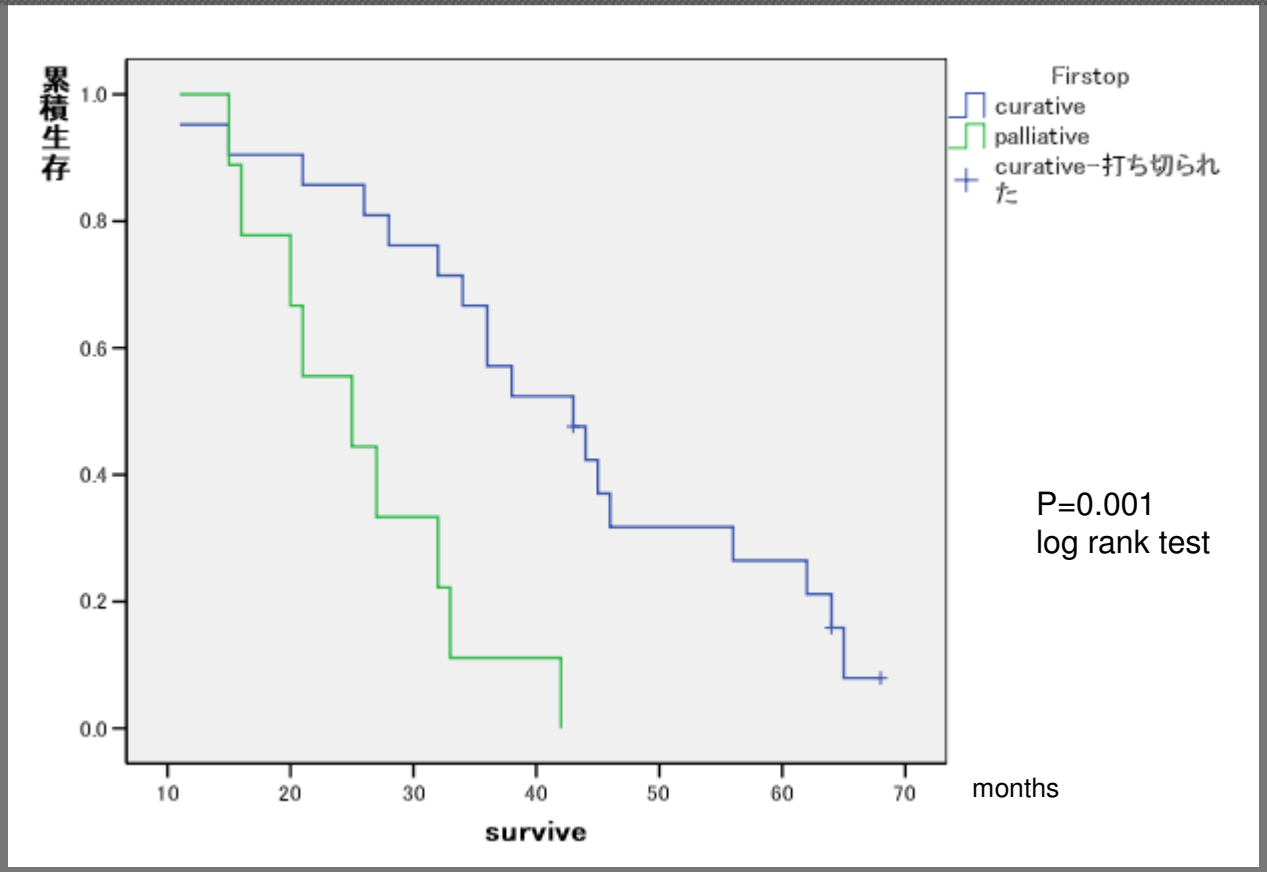
播種のない群で、有意に治療効果が良好であった。

Survival Rate



Estimated survival was 37.5months (95%CI：31.4-43.6)

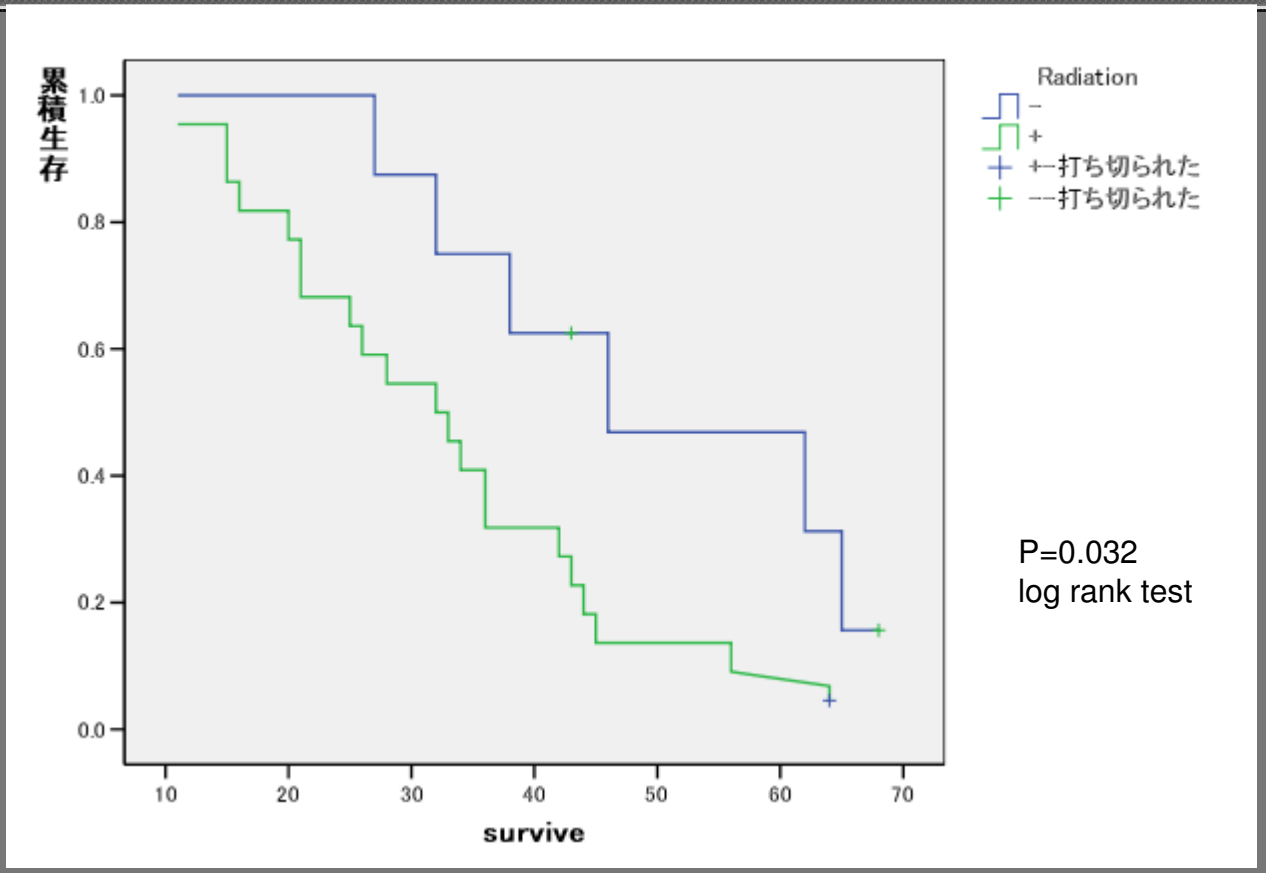
NIPP 前手術ごとの比較（curative vs palliative）



推定平均生存期間は

curative群　42.6ヶ月（35.2-49.9）
palliative群　25.7ヶ月（19.9-31.4）

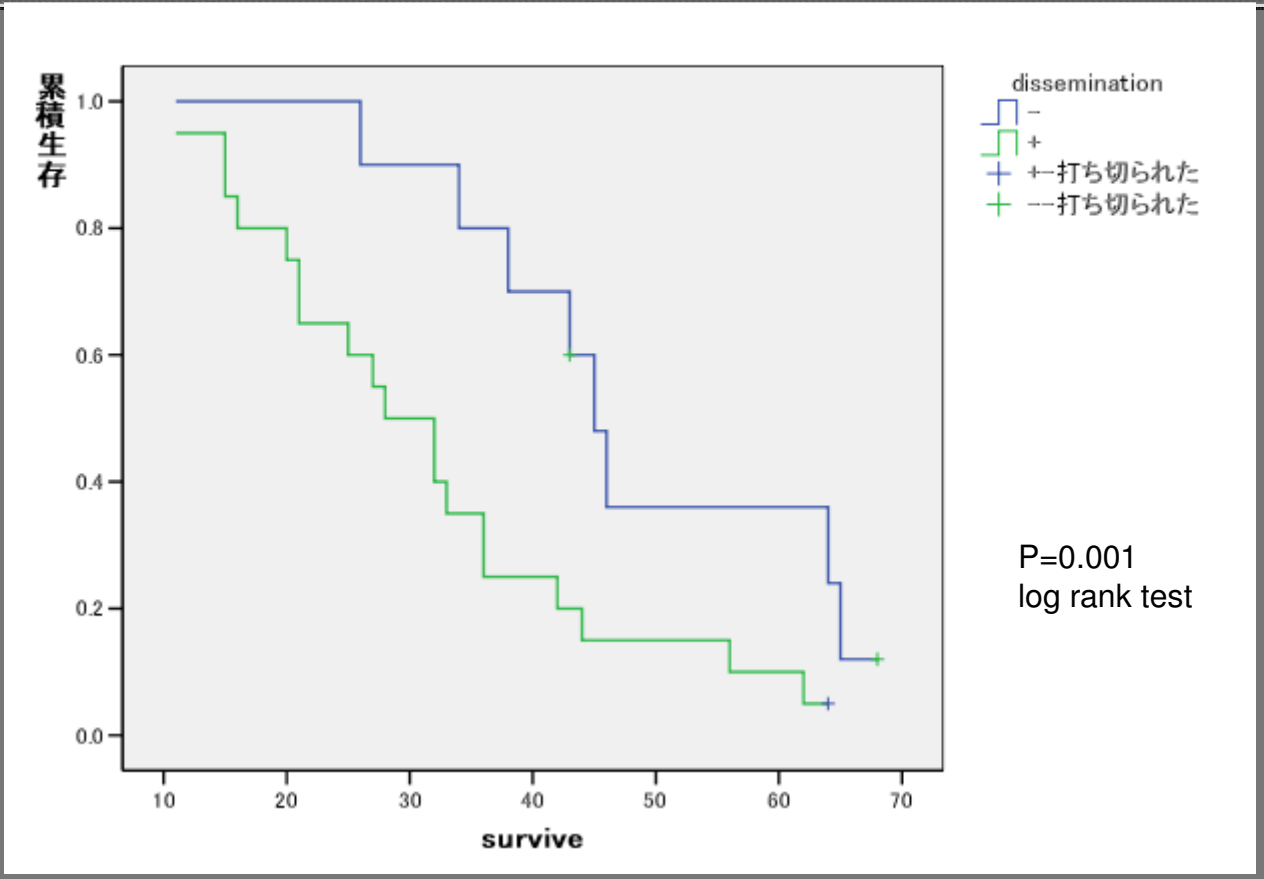
NIPP前、放射線治療



P=0.032
log rank test

推定平均生存期間は　　Radiation群　　33.0ヶ月（26.6-39.5）
non-Radiation群　　49.8ヶ月（38.9-60.7）

NIPP前の播種の有無

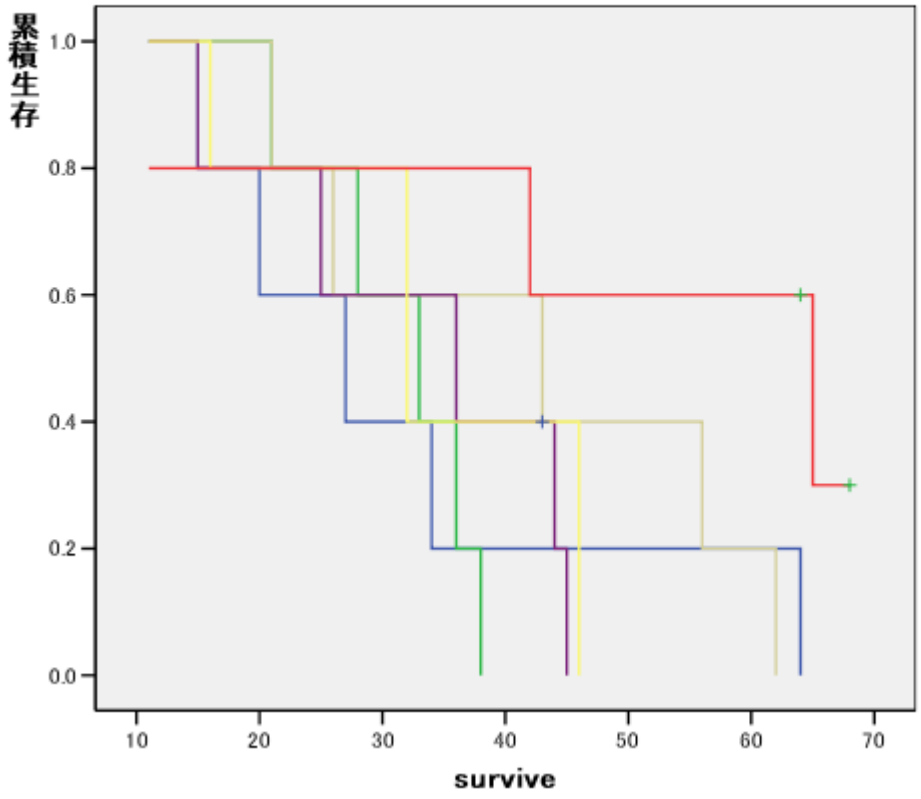


P=0.001
log rank test

推定平均生存期間は

Dissemination群	31.8ヶ月（25.2-38.4）
non-Dissemination群	48.7ヶ月（39.7-57.6）

CDDPによる分類

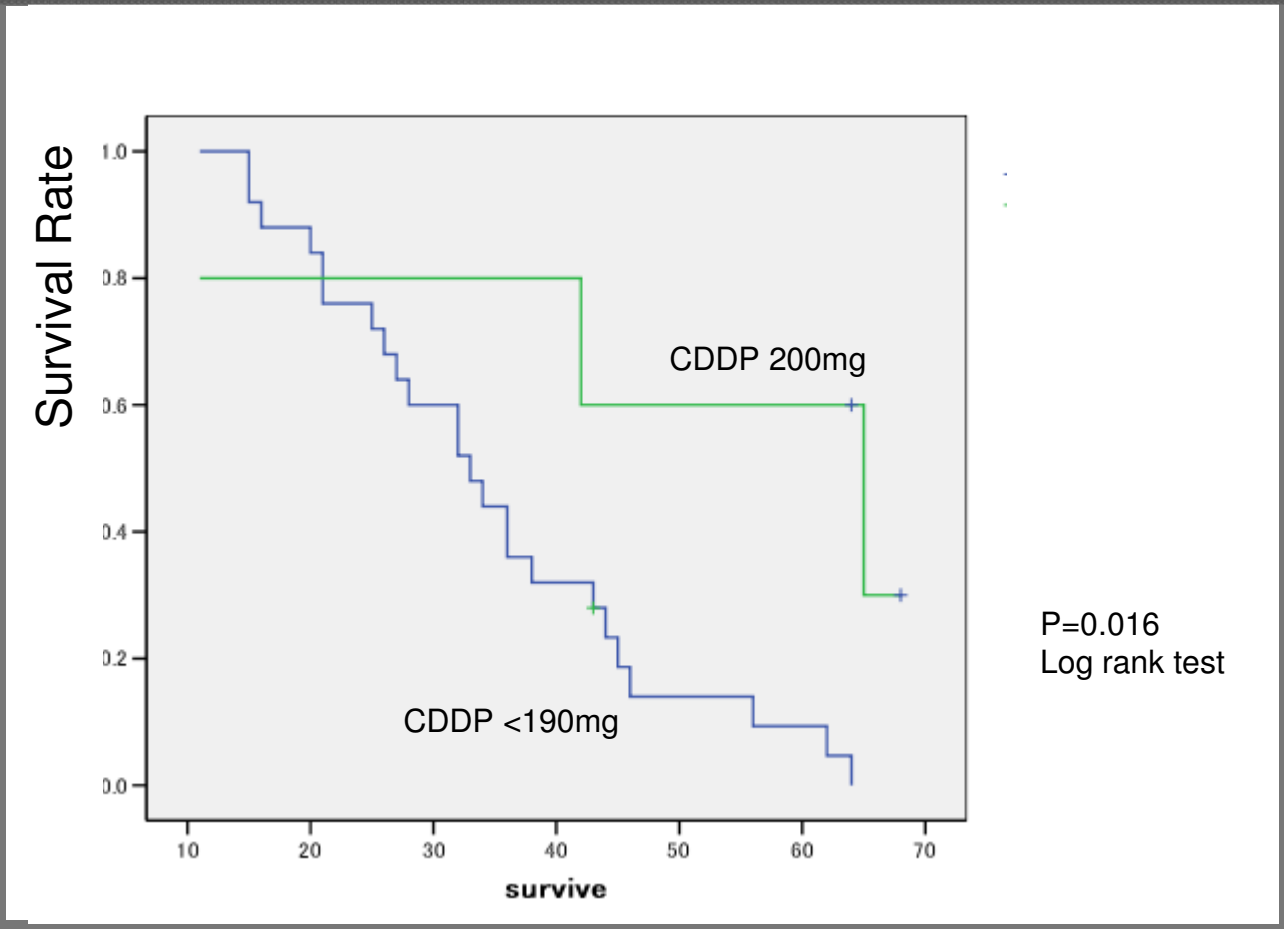


P=0.199
Log rank test

CDDP	平均推定予後
150mg	32.0ヶ月
160mg	31.2ヶ月
170mg	41.6ヶ月
180mg	33.0ヶ月
190mg	34.4ヶ月
200mg	50.5ヶ月

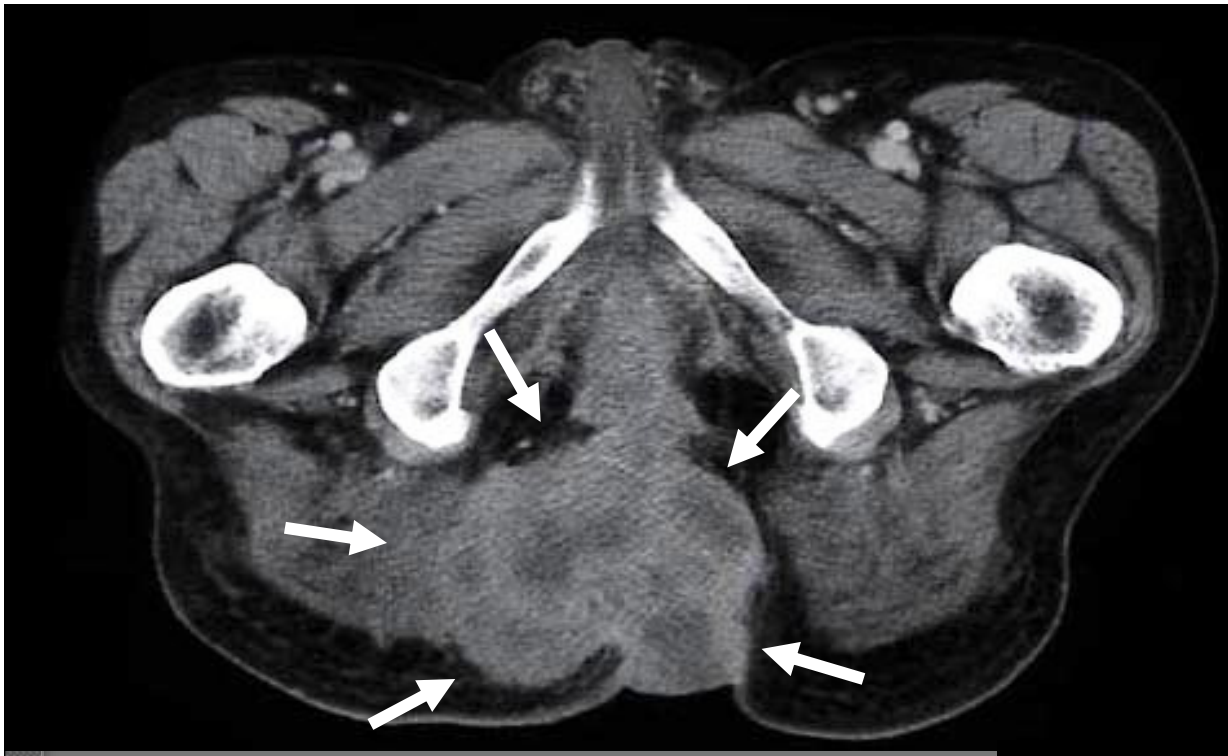
全体では有意差(P=0.199)は出なかった。
しかし、グラフを見ると200mg群で明らかに長い。そこで、、、

Survival Rate (200mg vs <190mg)



P=0.016
Log rank test

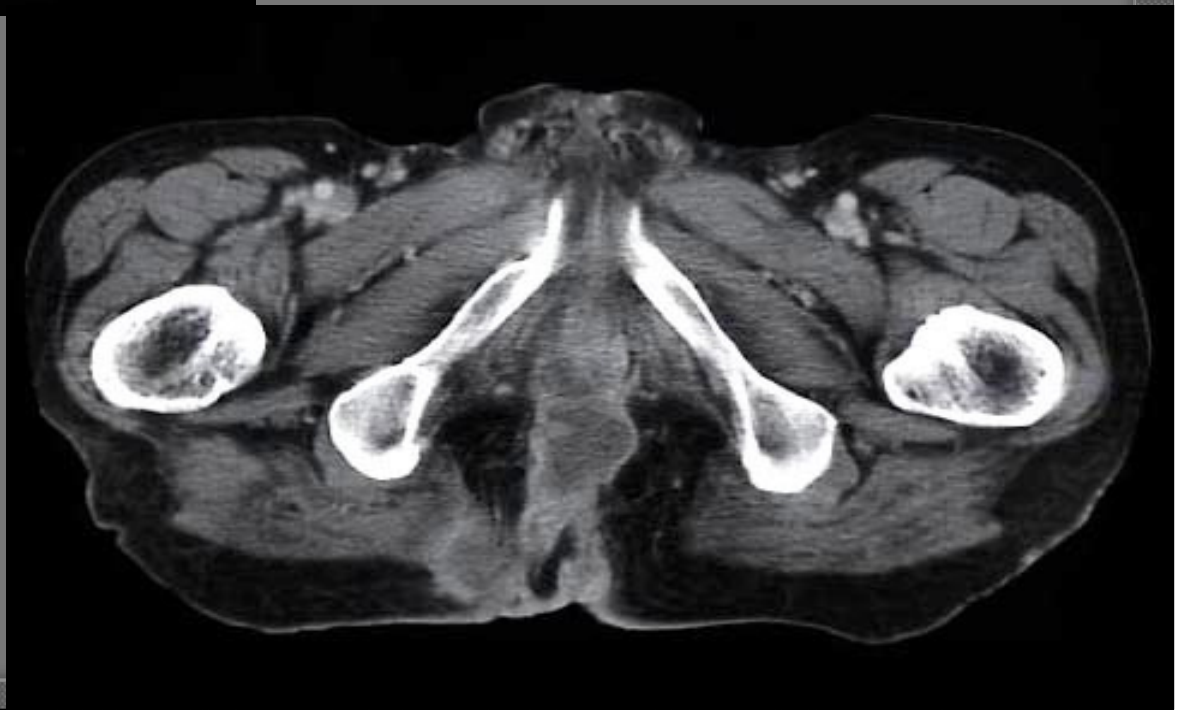
Estimated average survival	CDDP 200mg	50.5 months (31.3-69.7)
	CDDP <190mg	34.7 months (29.1-40.3)

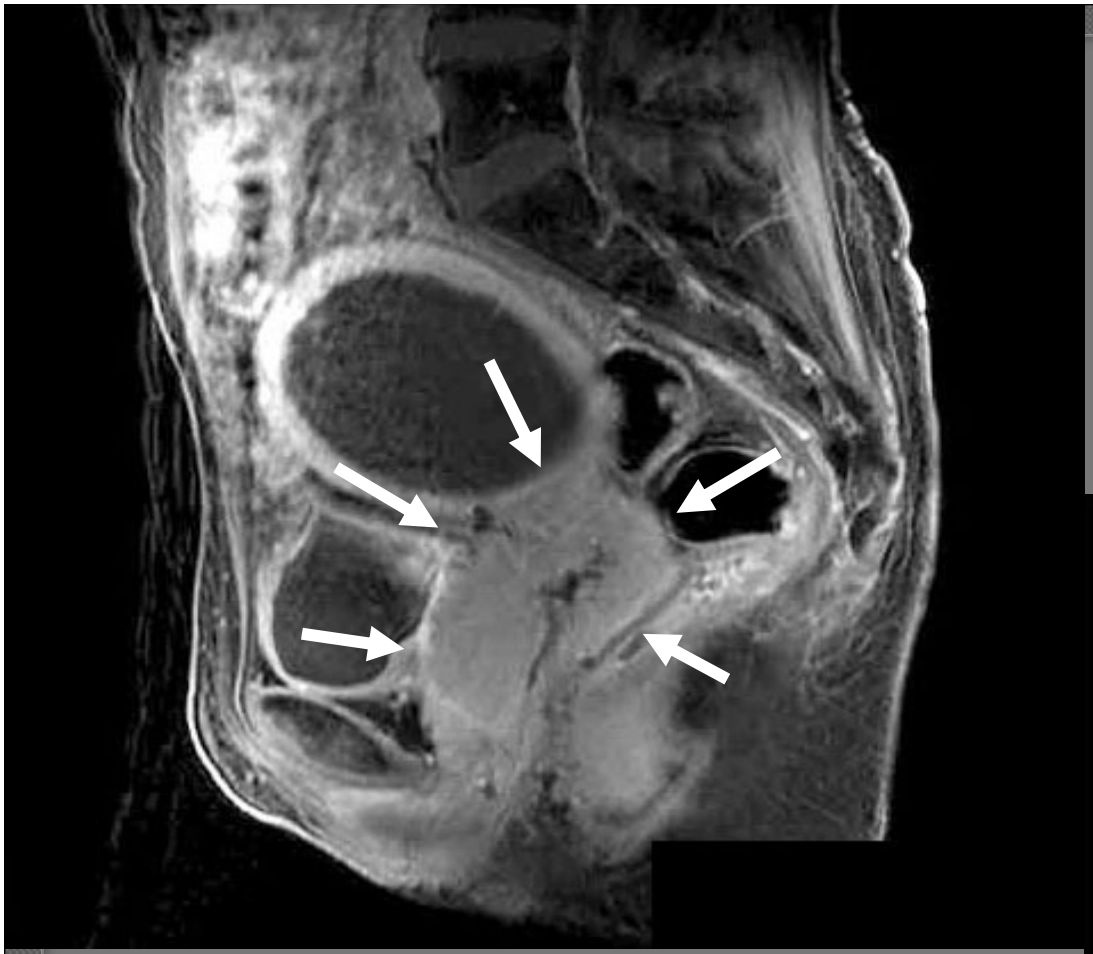


Before NIPP

53Y/O man,
Recurrent rectal cancer

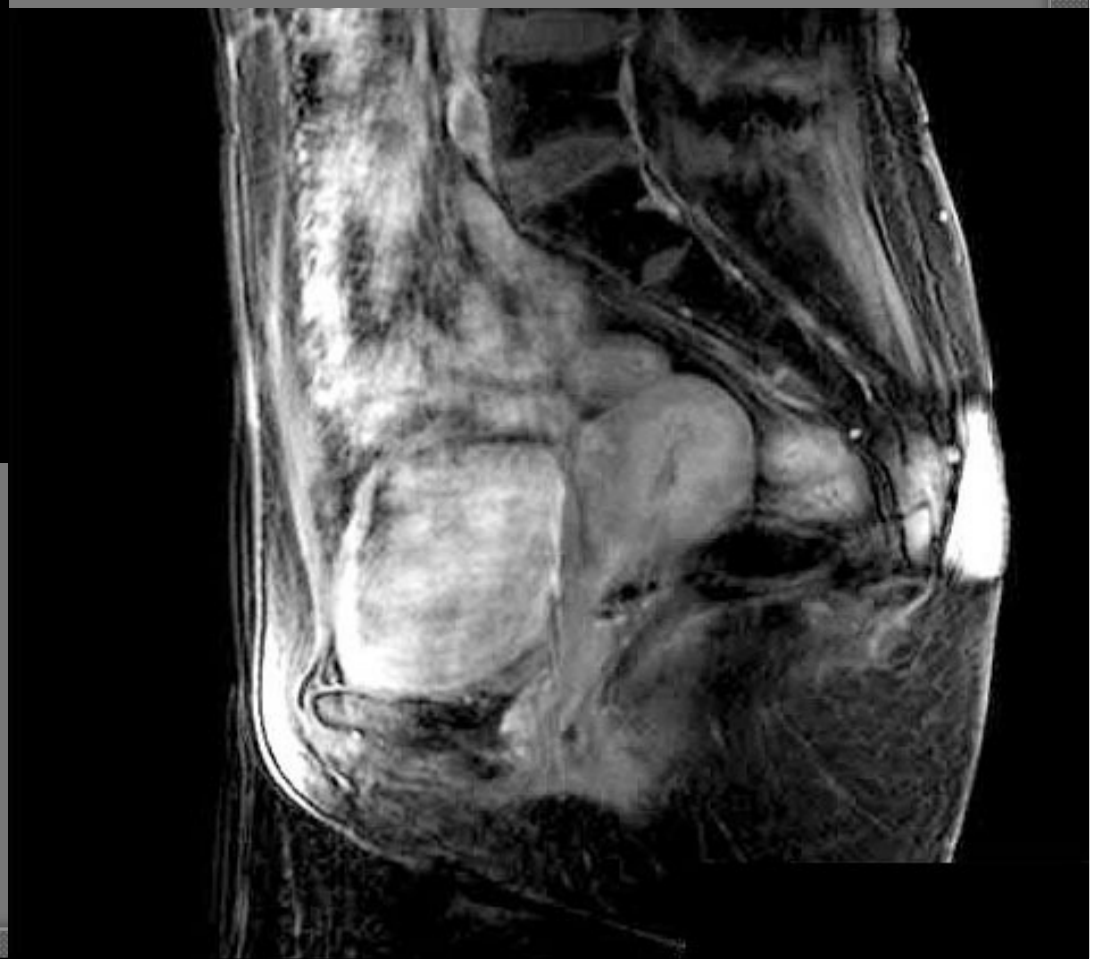
1.5 months after NIPP



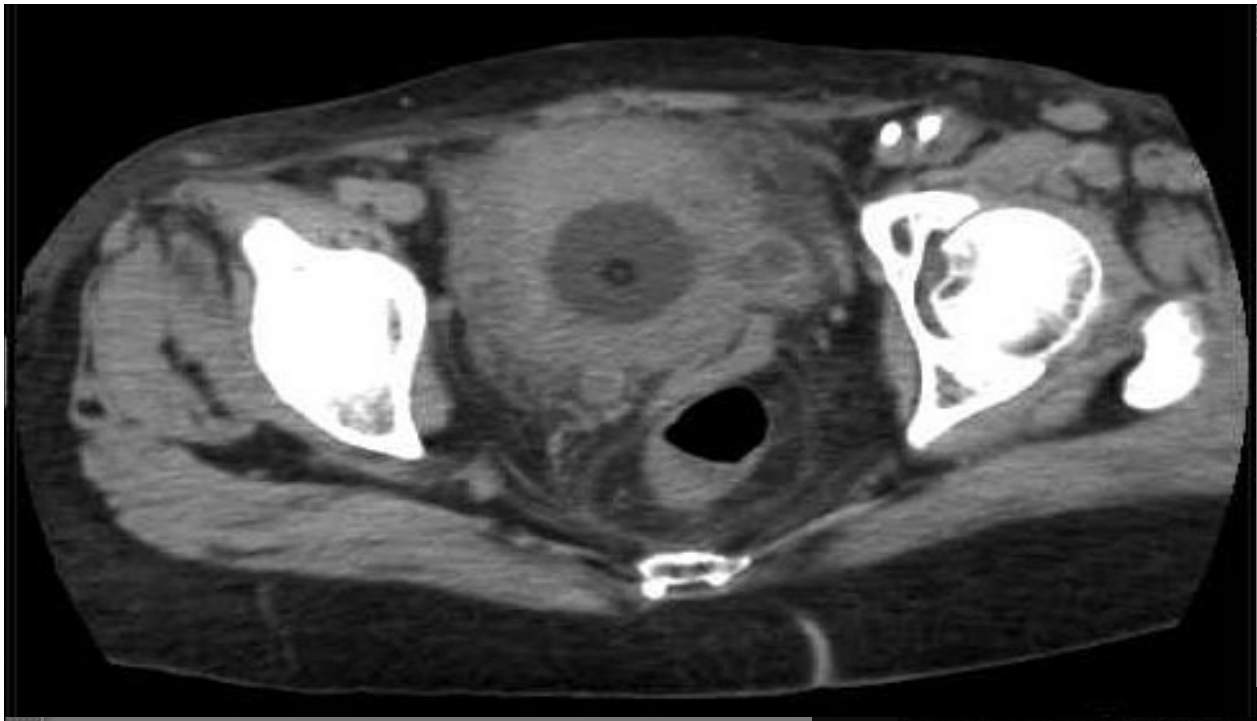


Before NIPP

54Y/O Female, cervical cancer
Stage IV

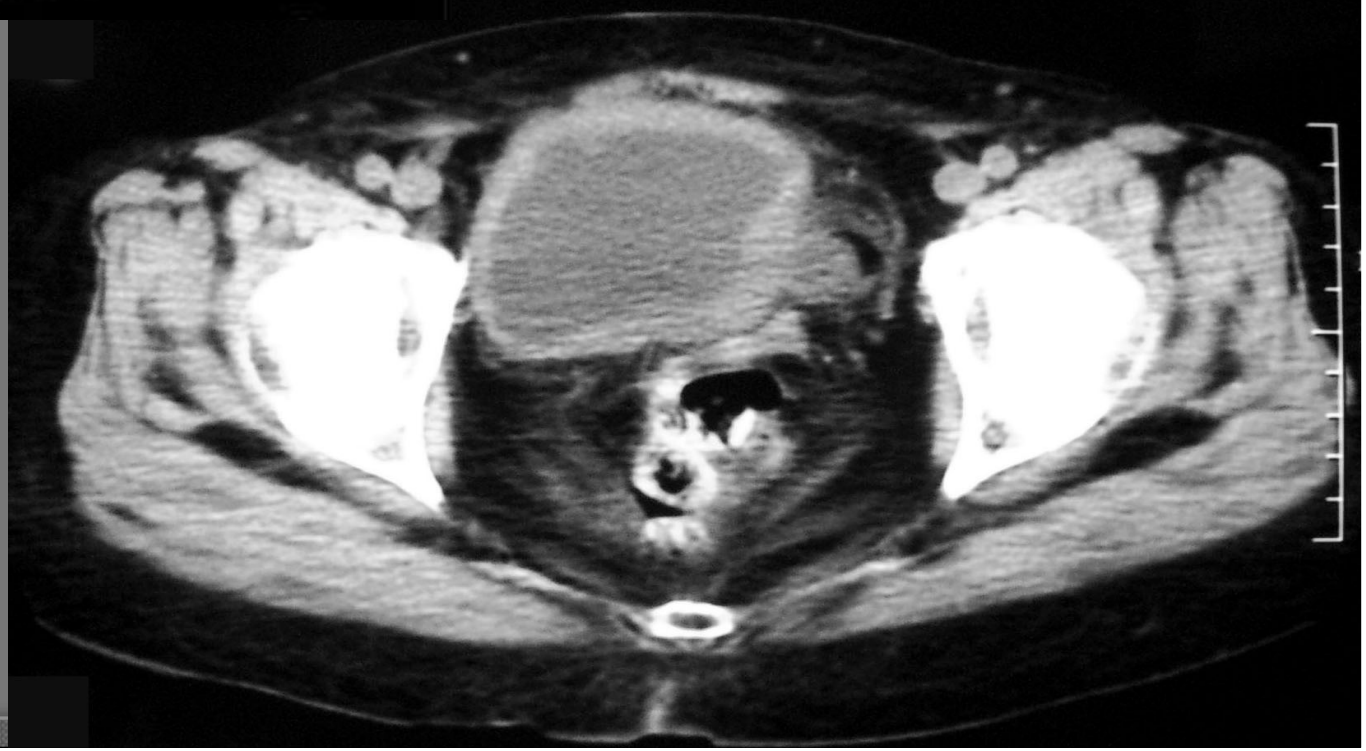


2 months later→
CR in MRI

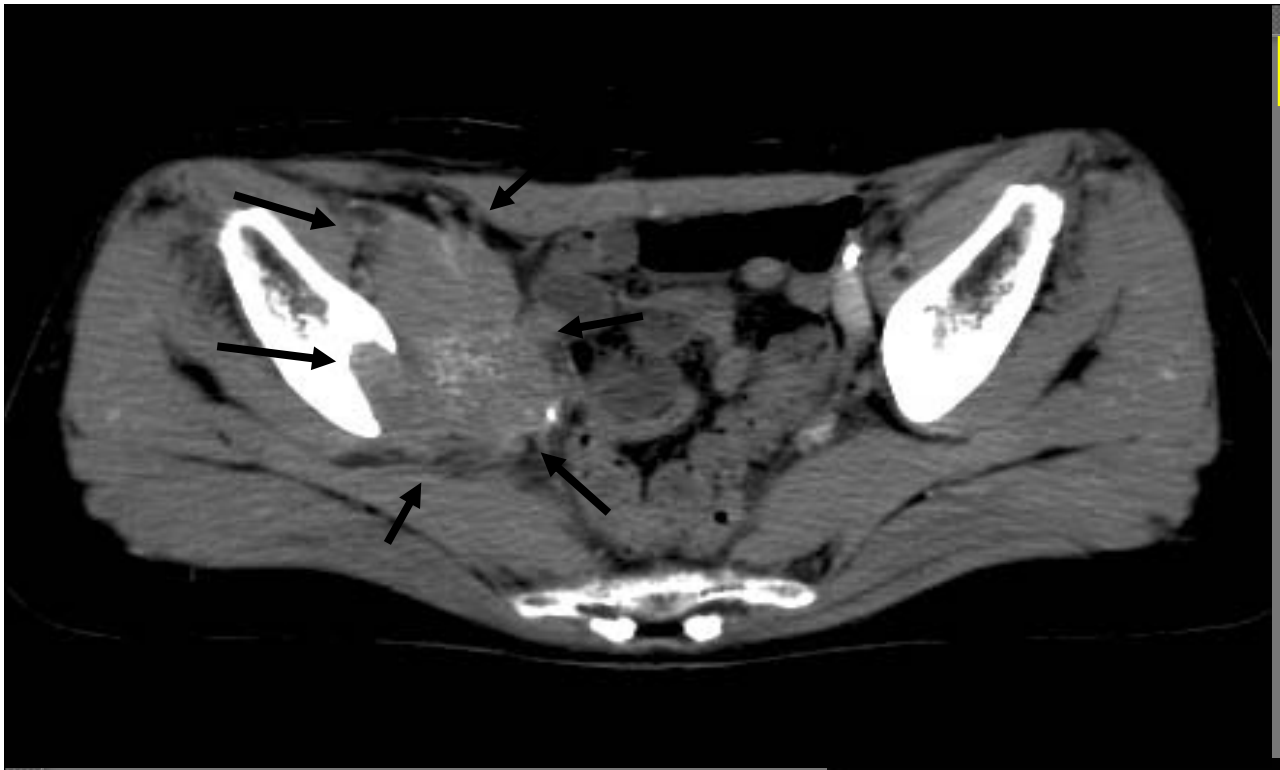


Before NIPP

68 Y/O Female
Invasive bladder tumor

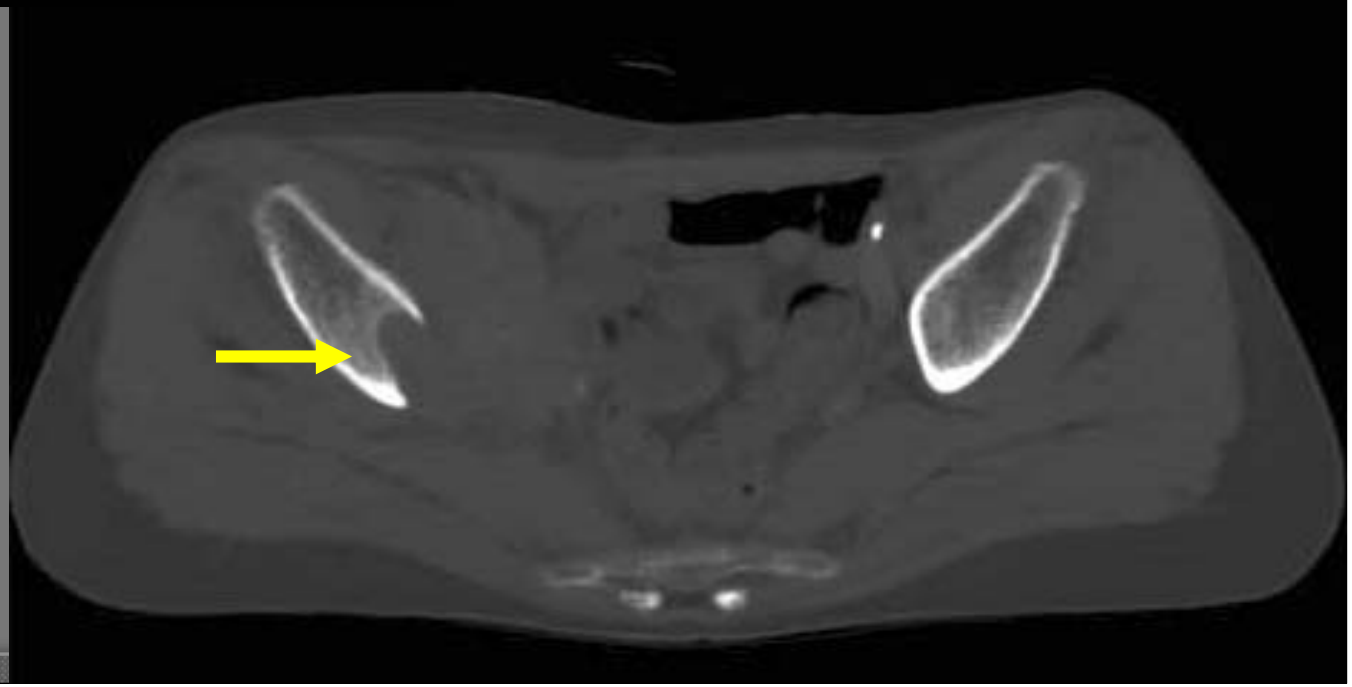


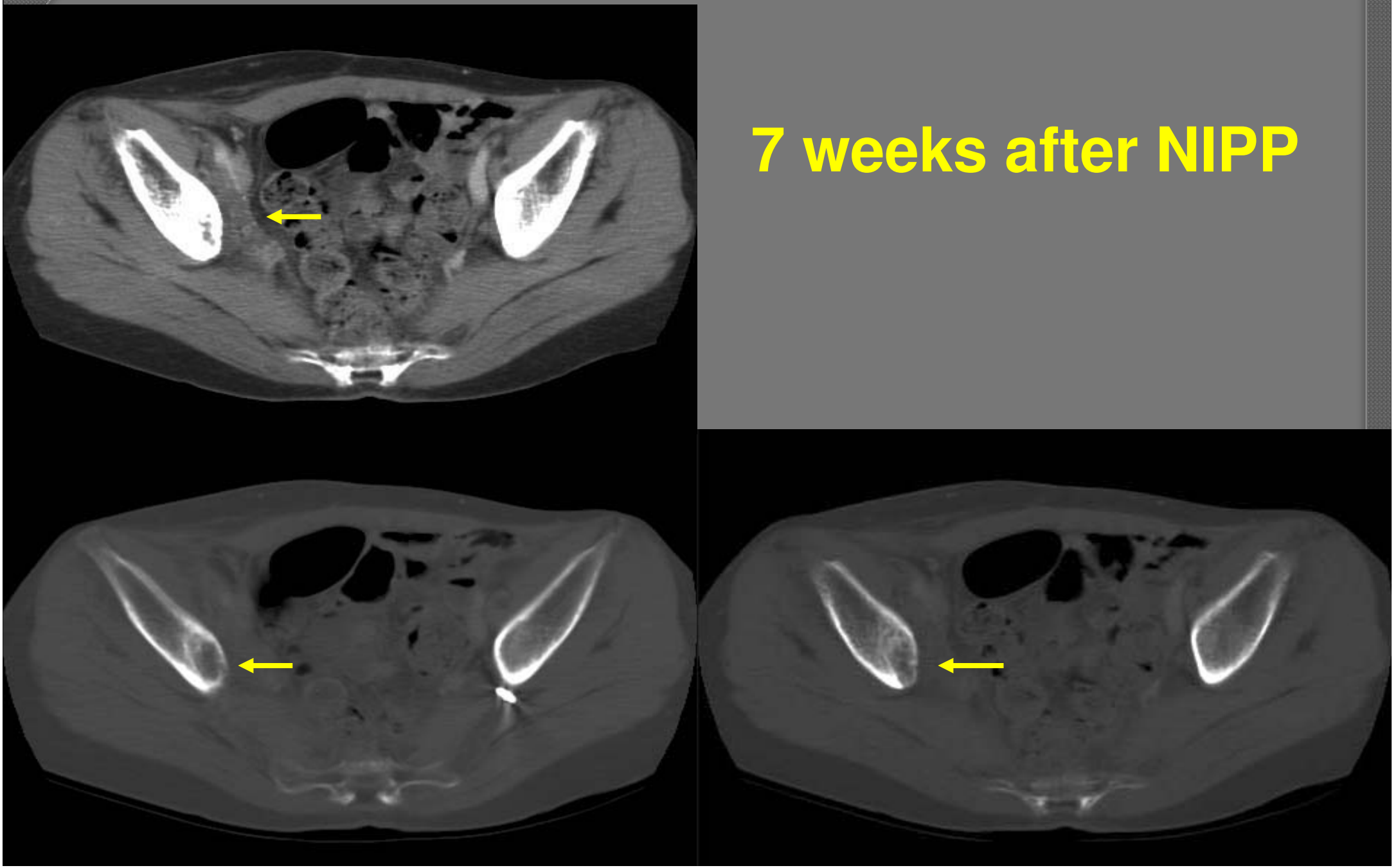
1.5 months later
CR in TUR-BT



Before NIPP

43 Y/O Female,
Cervical cancer




7 weeks after NIPP

Discussion

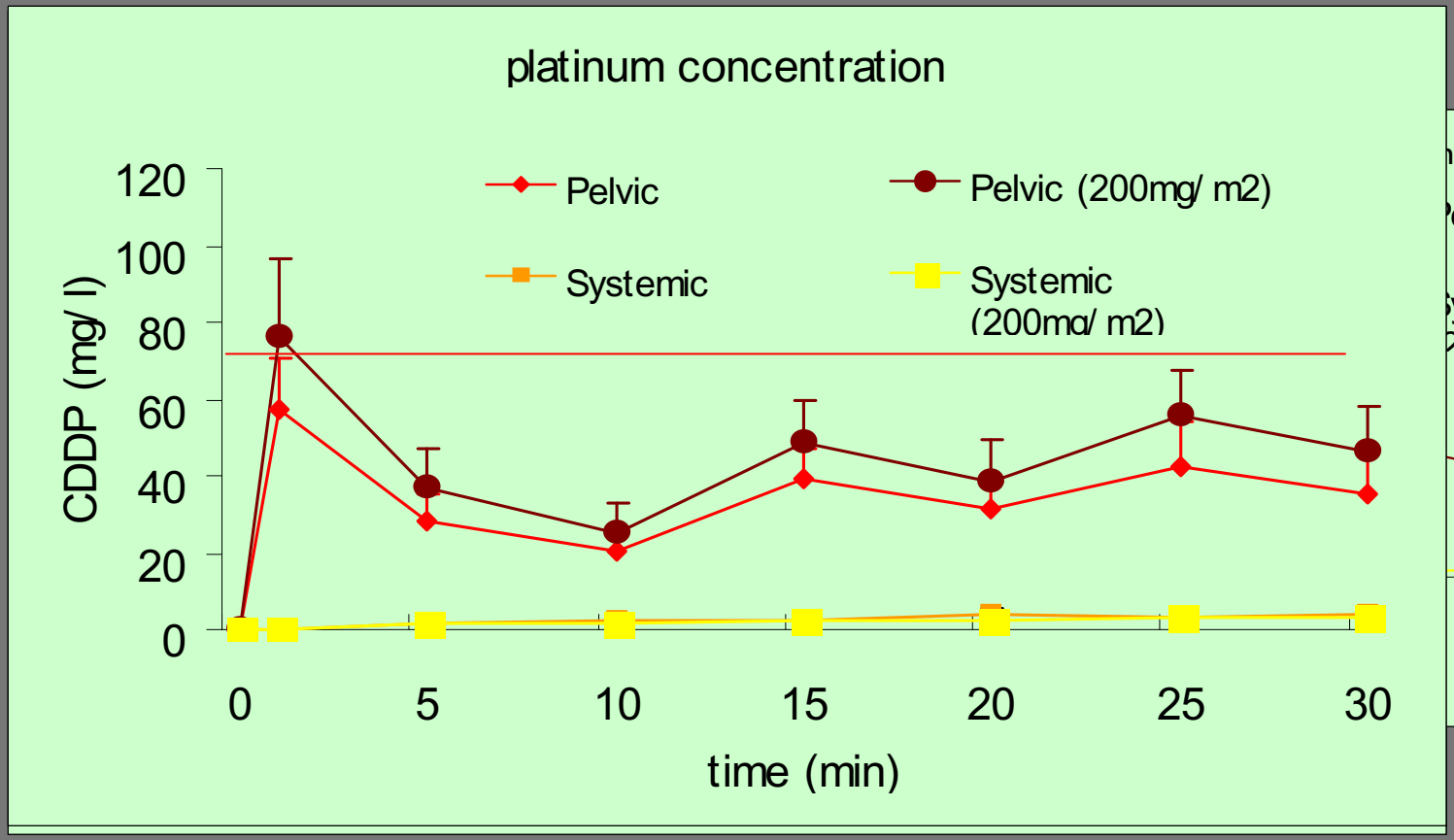
- During the NIPP, total isolated pelvic circulation is established. NIPP could decrease the leakage dramatically. And we can administer the massive dosage.

- Neuropathy was related with the dosage. However the maximum toxicity was grade II numbness. It could be admissible.
- The other toxicity was independent from the dosage and there was no more toxicity than grade III.

- Pain control was obtained even in the minimum dosage. NIPP can work well as a pain control. And also NIPP improved performance status.

- CDDP投与量が200mgを超えると有意に推定平均生存期間の延長が得られた。200mg投与群では最大血中濃度が十分に高くなるためと考えられた。
- In group of 200

CDDP concentration



IC50 value for gastrointestinal cancer **10.7 mg/L** **in the sensitive tumor**
71.2 mg/L **in the resistant tumor**

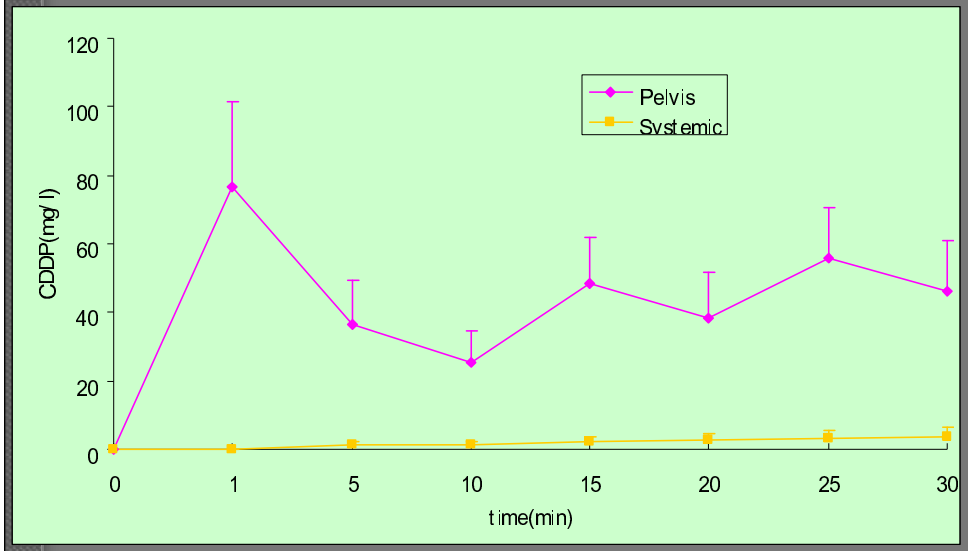
Limitation

- 症例数が30例と少ない
- NIPP前の条件にばらつきがある
- 播種症例が多く、予後を純粋に評価し得ない
- CDDP投与量を上昇させるために、神経毒性のコントロールを考える必要がある

Conclusion

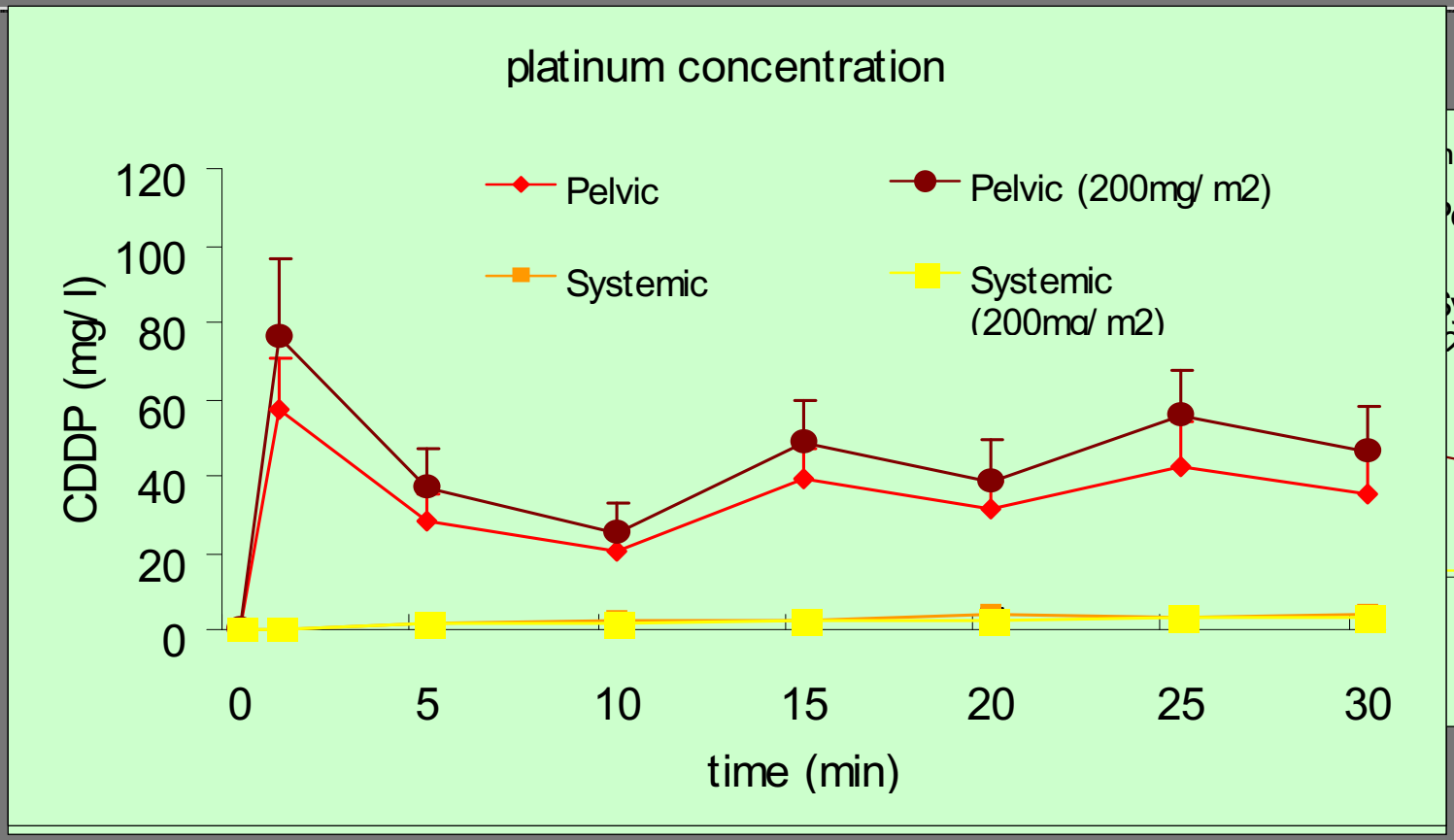
- NIPP therapy may be able to a safely deliver high-dose regional chemotherapy and effectively control tumor growth in patients with inoperable rectal cancer.

結果：NIPP中CDDP濃度



全区間において骨盤内濃度は有意に（P<0.001）に上昇

NIPP中platinum濃度



全区間において骨盤内濃度は有意（P<0.001）に高値であった