

Recent advances in the treatment of peritoneal metastasis from gastric cancer

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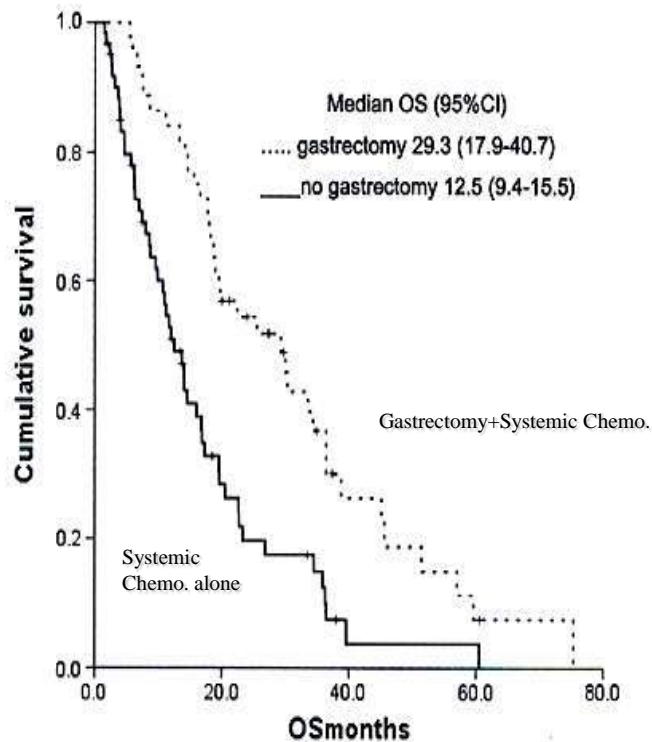
Development of innovative treatments for peritoneal metastasis from gastric cancer

- Hyperthermic intraperitoneal chemo-perfusion (**HIPEC**)
Spratt JD: Cancer Res, 40;256:1980: 1975
Koga S: CHIPC vs. non-HIPC (RCT); Cancer, 73:2048:1990
- New chemotherapeutic drugs and combination chemotherapy: Late 1990s
S1, paclitaxel, docetaxel, irinotecan
Molecular target-based drugs: Herceptin, Ramcirumab
- New surgical technique for complete removal of PM : **Peritonectomy**
Sugarbaker PH, Ann Surg. 221;29:1995
- Early postoperative intraperitoneal chemotherapy (**EPIC**)
Yu WS, RCT: Ann Surg, 226:347:1998
- Comprehensive treatment (**Peritonectomy combined with POC**): 1999
PSOGI Group: Sugarbaker PH, Heald B, Gilly F, Piso P, Deraco M, Zoetmulder FAN, Moran B, Gonzalez MS, Yonemura Y.
- IP chemotherapy using **Taxans**
Fushida S, Gan to Kagaku. 29;1759: 2002,
Cancer Chem. Pharmacol, 71:1265:2013
- Neoadjuvant intraperitoneal/systemic Chemotherapy (**NIPS**)
Yonemura Y, EJSO. 32; 661:2006.
- Extensive intraperitoneal lavage (**EIPL**)
Kuramoto M, Shimada: Ann. Surg. 250:242: 2009.
- Laparoscopic HIPEC
Sommariva A, Ann Surg Oncol, 19;3737:2012.
Yonemura Y, Ann Surg Onco. 24;478:2017.

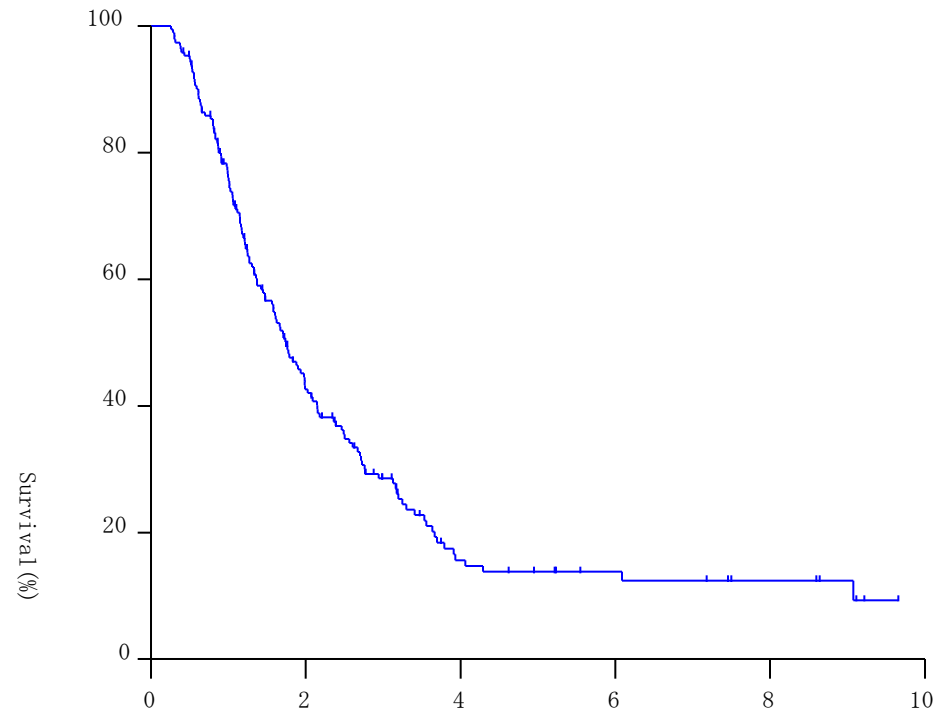
Survival of GC patients with PM treated by systemic chemotherapy alone and NIPS+CRS+HIPEC

Gastric cancer 16:290-300: 2013
Treated by systemic chemotherapy alone.
VS. + gastrectomy

Yonemura Y [Eur J Surg Oncol.](#) 2015;41:911-9
NIPS+CRS+HIPEC

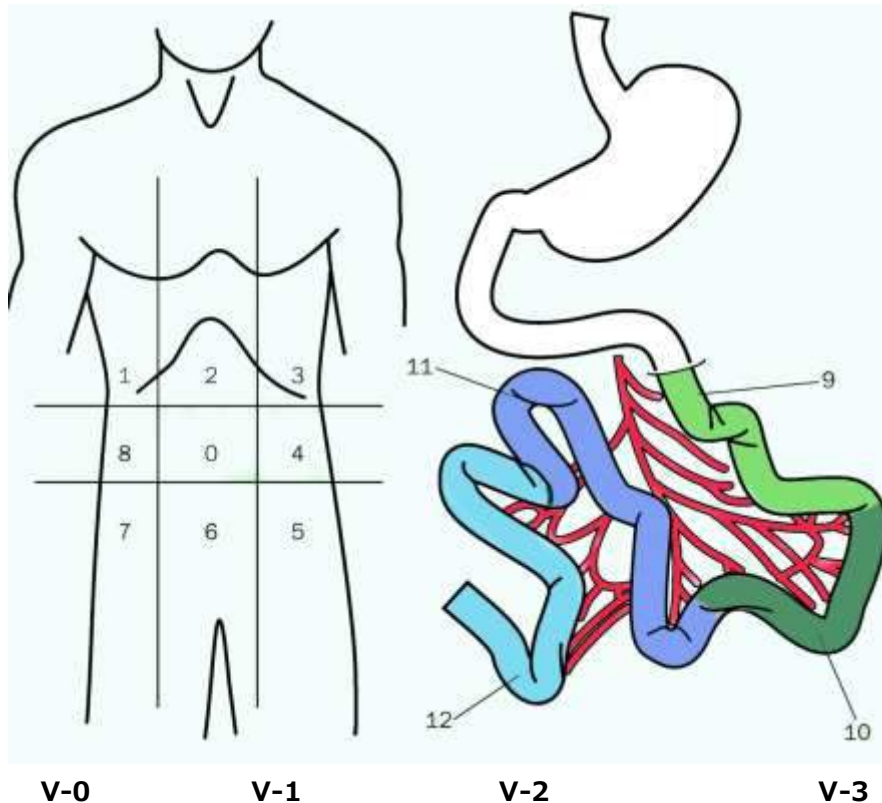


	MST	5-YSR	DFS after5-Y
Systemic chemo	12.5M	3%	0
+gastrectomy	29.3M	10%	0



	MST	5-YSR	DFS after5-Y
NIPS+CRS	21M	145	15

Peritoneal Carcinomatosis Index (PCI) for the spread and size of PM and completeness of cytoreduction



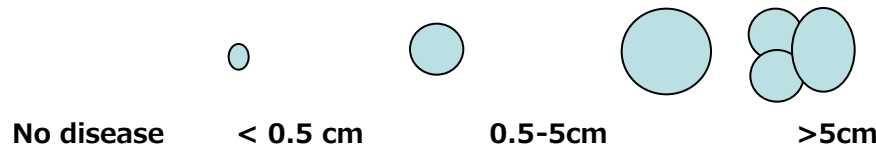
Region	lesion size
0 Central	3
1 Right upper	3
2 Epigastrium	3
3 Left upper	3
4 Left flank	3
5 Left lower	3
6 Pelvis	3
7 Right lower	3
8 Right flank	3
9 Upper jejunum	3
10 Lower jejunum	3
11 Upper ileum	3
12 Lower ileum	3

PCI 39

Lesion size score

LS 0 no tumor seen, LS 1 < 0.5 cm

LS 2 0.5 ~ 5 cm, LS 3 > 5 cm



Completeness of cytoreduction

CC-0: complete resection

CCR-0

CC=1:residual disease:<0.5cm

CC=2:0.5cm~5cm

CCR-1

CC=3:=<5cm

- A. G Portilla et al. The intraoperative staging systems in the management of
B. Peritoneal surface malignancy. (J Surg Oncol. 2008;98:228-231):

Concept of comprehensive treatment with intent of cure

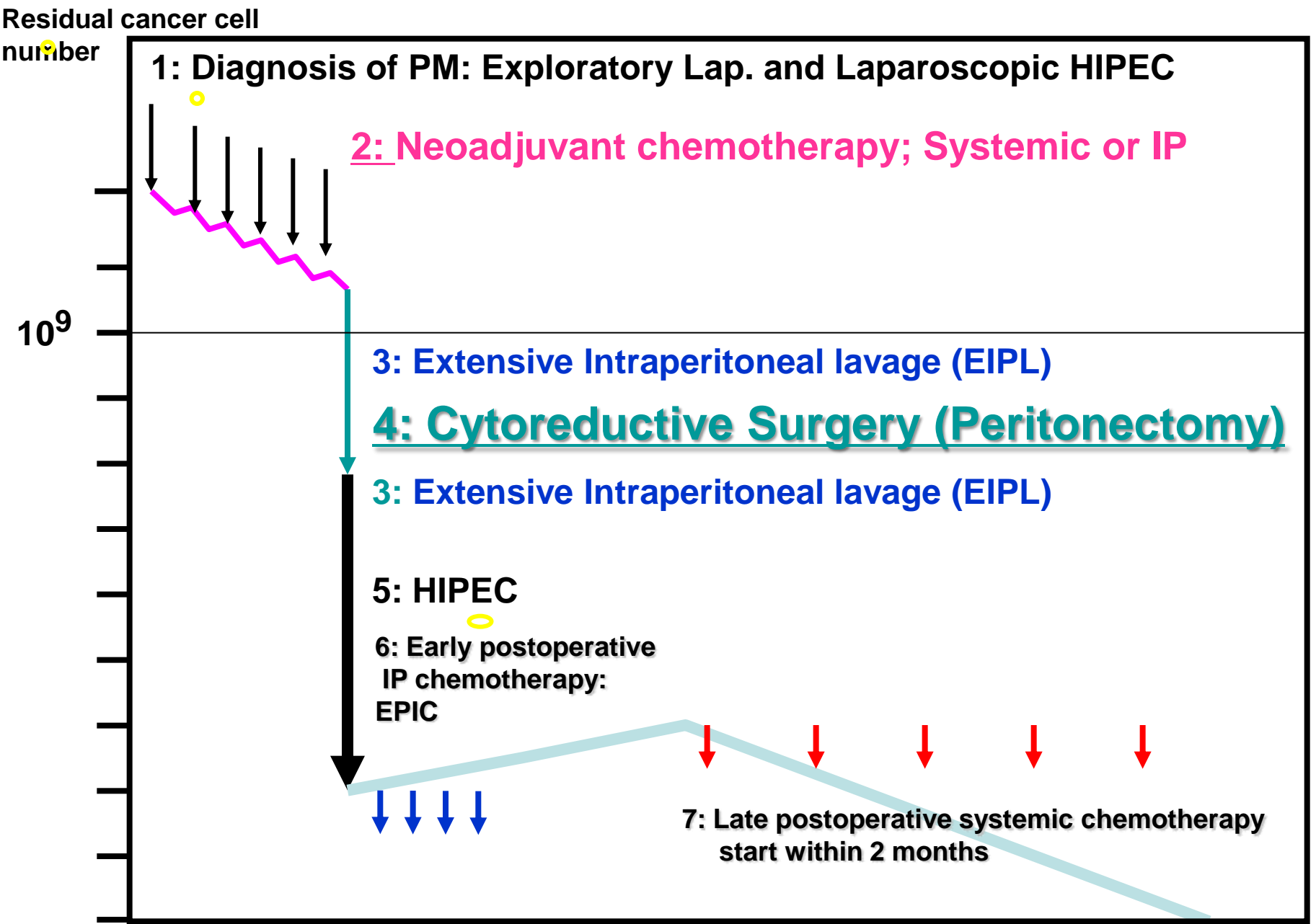
1: Complete removal of macroscopic PM,

2: Eradication of micrometastasis,

by perioperative chemotherapy

NAC, NIPS, HIPEC, EPIC, late postope. Chemo.

Comprehensive treatment for PM patients with curative intent



Preoperative assessment of volume and distribution of peritoneal metastasis and detection of patients with low PCI

**CeCT, MRI and PET CT are powerless to detect
small peritoneal metastasis**

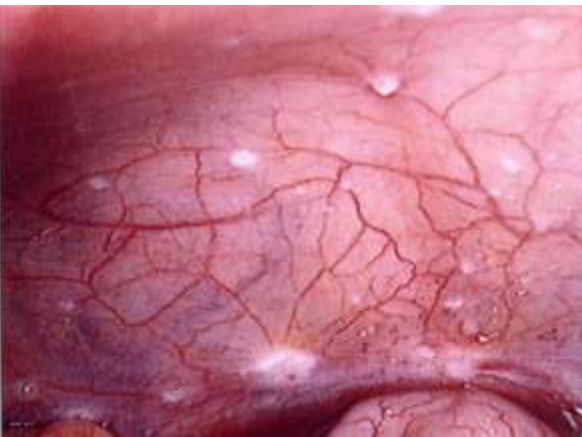
CeCT smaller than 5 mm: sensitivity 11%

Larger than 5cm: sensitivity 94%

(Koh JL, Ann Surg Oncol; 16:327, 2009)



**Exploratory laparoscopy:
Cytologic exam, histologic exam.
IP port placement
Laparoscopic HIPEC**



Role of Neoadjuvant intraperitoneal/systemic chemotherapy (Bidirectional chemotherapy) (NIPS)

a peritoneal port
system

Wash cytology and
chemotherapy
through port system

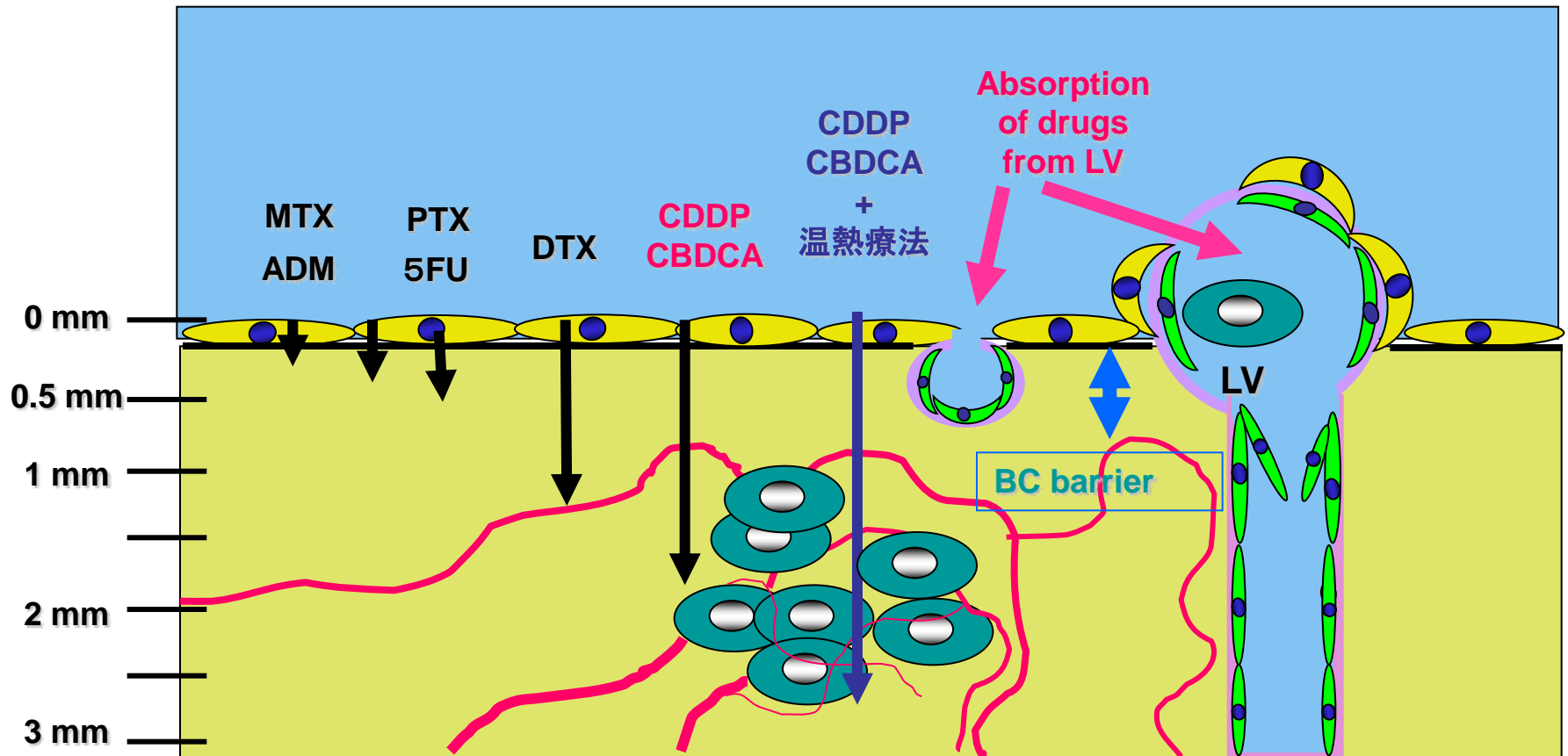


The effective diffusion distance into subperitoneal tissue in IP chemotherapy

Yonemura Y: *cancer Let*:161:189-196:2004

Shimada T; et al: *J Pharam Pharmacol*: 57;177-181;2--5

Penetration distance of anti-cancer drugs from peritoneal surface Absorption of drugs through subperitoneal lymphatic vessels



Each drug has its own penetration depth into the peritoneal surface, and the effective diffusion distance into tissues reportedly ranges from 100 μ m to 2000 μ m in IP chemotherapy

IP chemotherapy eradicates PFCCs and cancer cells growing on mesothelial cells, in the lymphatic vessels and in the superficial layer of submesothelial tissue.

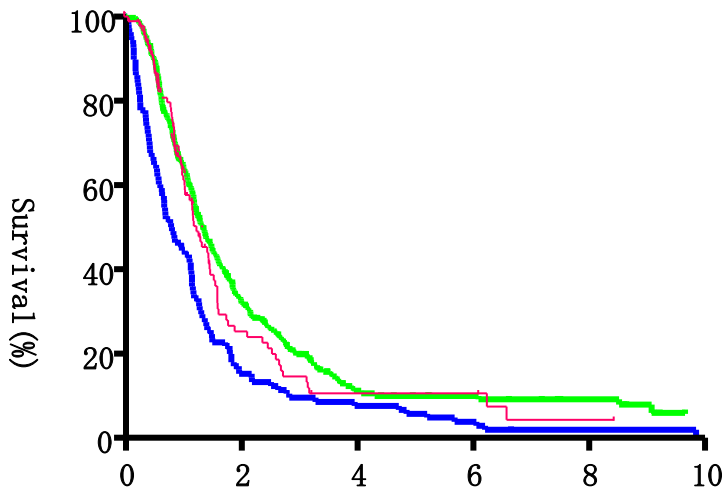
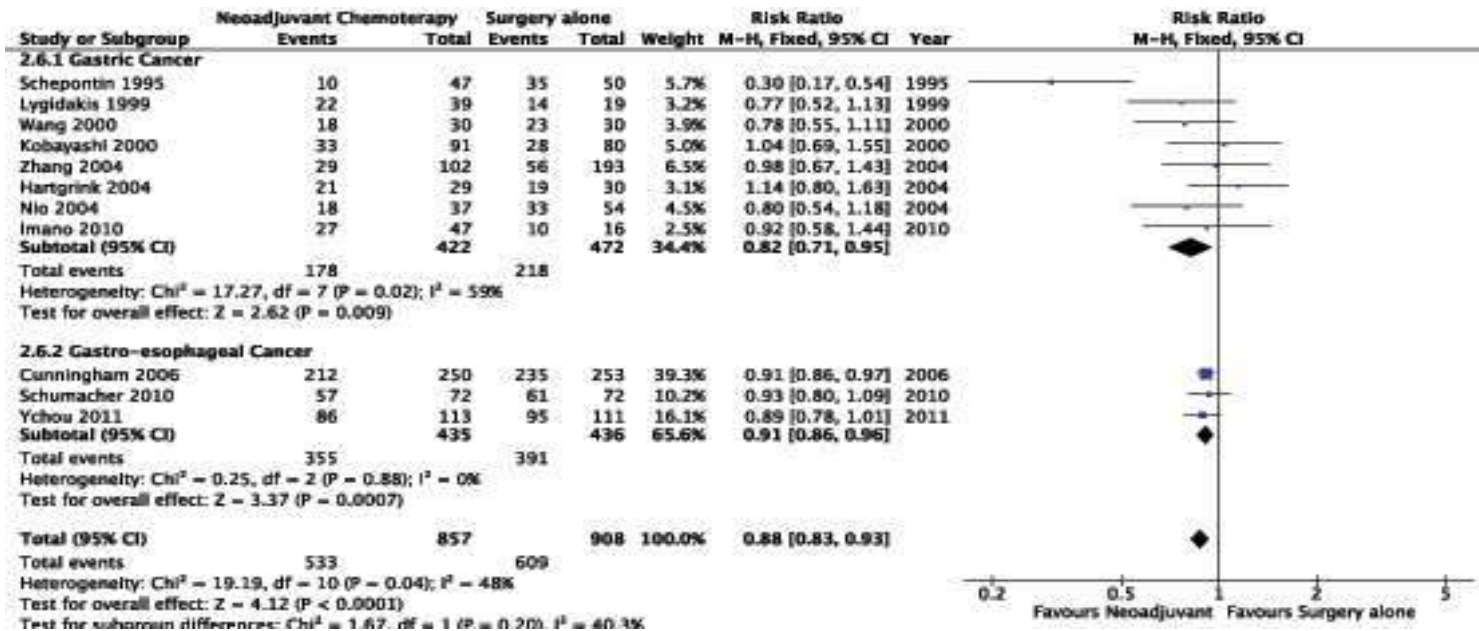
Factors limiting the success of IP chemotherapy include the presence of adhesions around the tumors and deep-seated tumor cells.

Molecular weight, AUC ip/p, enhanced cytotoxicity combined with hyperthermia, penetration distance into subperitoneal tissue

Drugs	MW	pAUC/aAUC	Enhanced sensitivity with heat	Penetration distance
Doxorubicin	380	230	Yes	6 cell layers
Melphalan	305	93	marked	NE
MMC	334	33	Yes	2 mm
CDDP	300	7.8	Yes	1-3 mm
Gimcitabine	299	500	Yes	NE
Mitoxantrone	517	115	Yes	6 cell layers
Oxaliplatin	397	16	Yes	2 mm
Etoposide	568	65	Yes	NE
Irrinotecan	677	N/A	No	NE
PTX	853	1000	No	80 cell layers
DTX	861	552	Yes	1.4 mm
5-FU	130	250	Yes	0.2 mm
Carboplatin	371	10	Yes	2 mm

Meta-analysis of RCT to evaluate NAC on outcome after CRS.

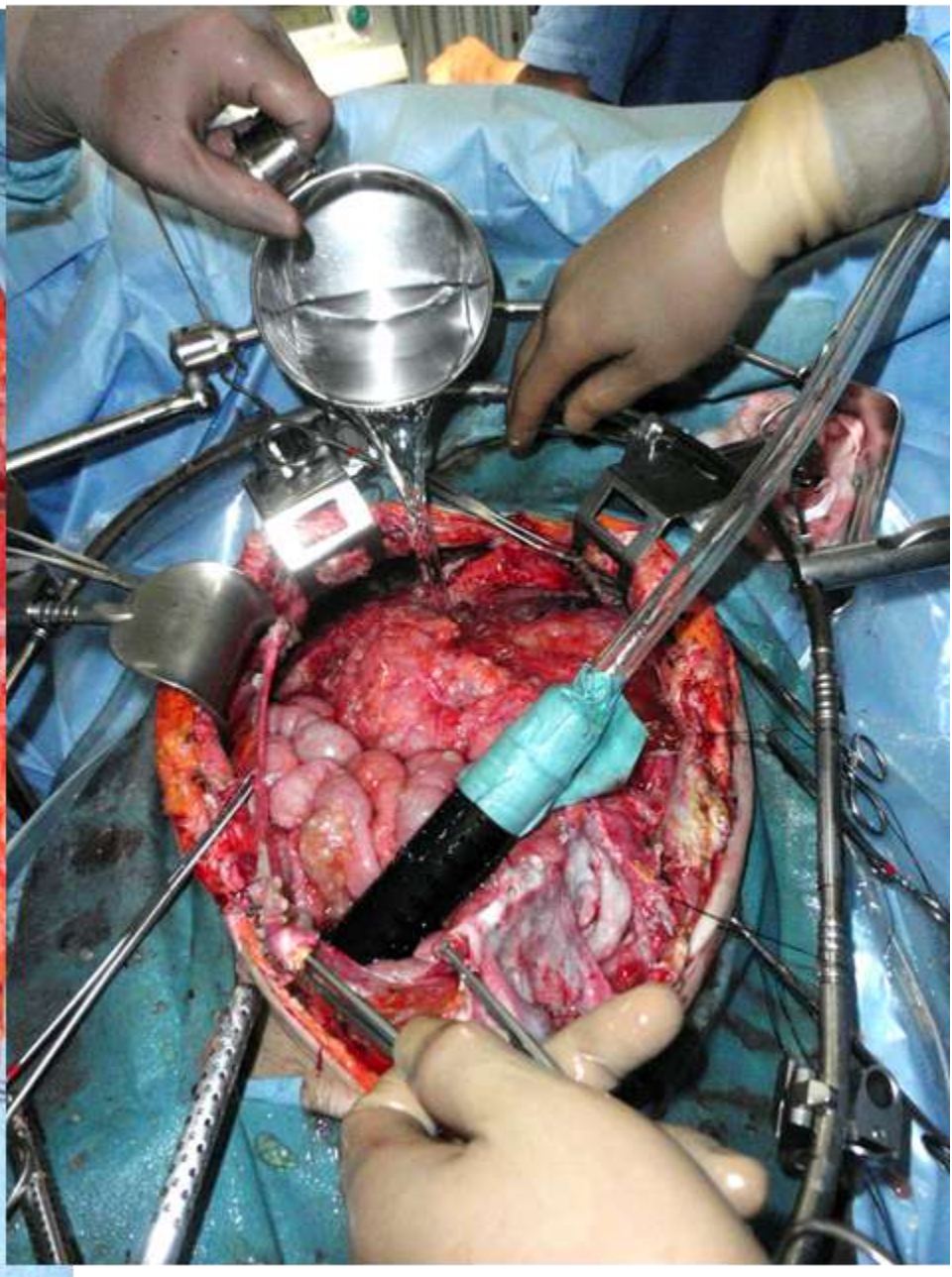
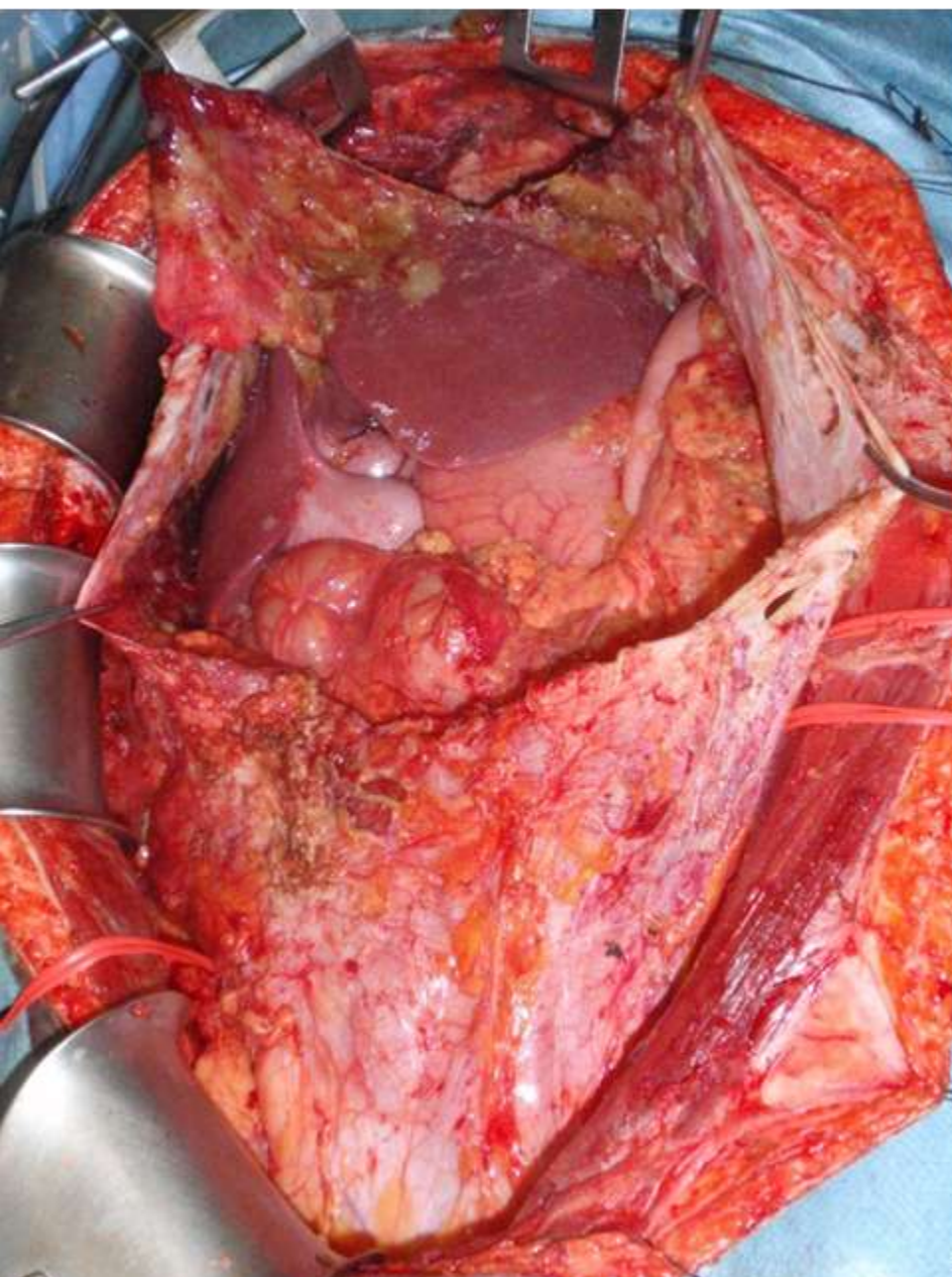
PSOGI study: 2001 patients from 15 RCT 907 NAC+ CRS vs. 1024 CRS
 NAC+CRS reduces the overall mortality at 5-year (RR=0.88), Morbidity and perioperative mortality rate are not influenced by NAC. Cocolini et al.



Yonemura Y			
	No. of cases	MST	
No NAC	108	9M	} $P < 0.001$ NS
NIPS	313	16m	
Systemic NAC	90	14m	

Extensive intraoperative peritoneal lavage (EIPL): Saline 1Lx10

Kuramoto M, Shimada S, et al. Ann. Surg. 250: 242-246; 2009.



Peritonectomy techniques

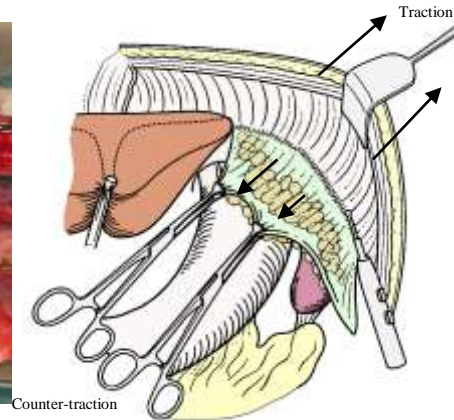
Ball tip electorocuttery
Under high power
Electrosurgery (100 W)



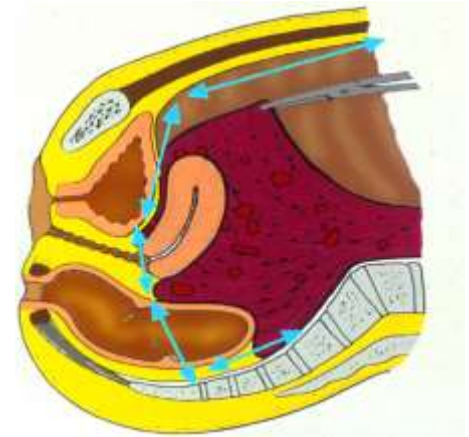
Argon Beam Coagulator
ABC for hemostasis
electroevaporation



Peritonectomy for
Upper quadrant



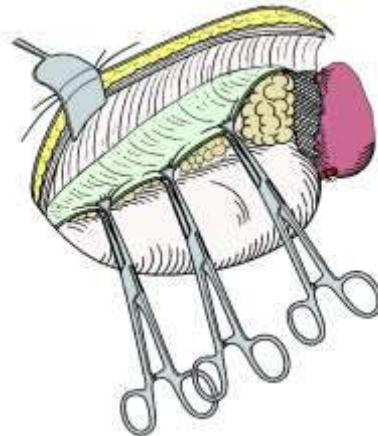
Pelvic peritonectomy



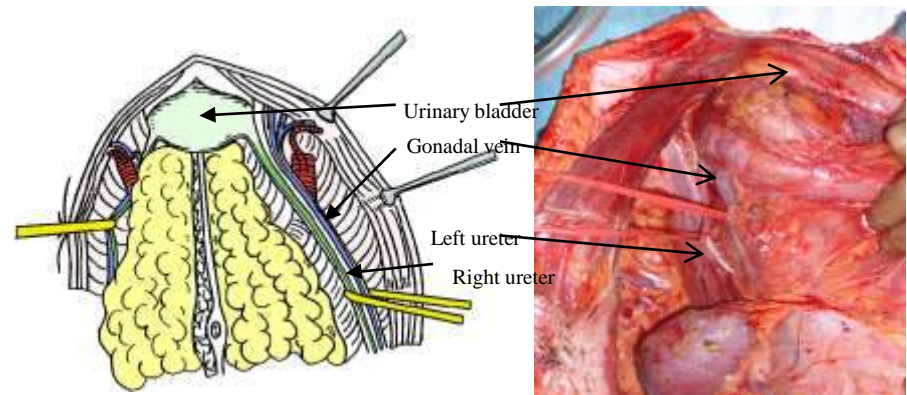
Peritonectomy for
Morrison pouch and
Right hemidiaphragm



Peritonectomy for
parietal peritoneum

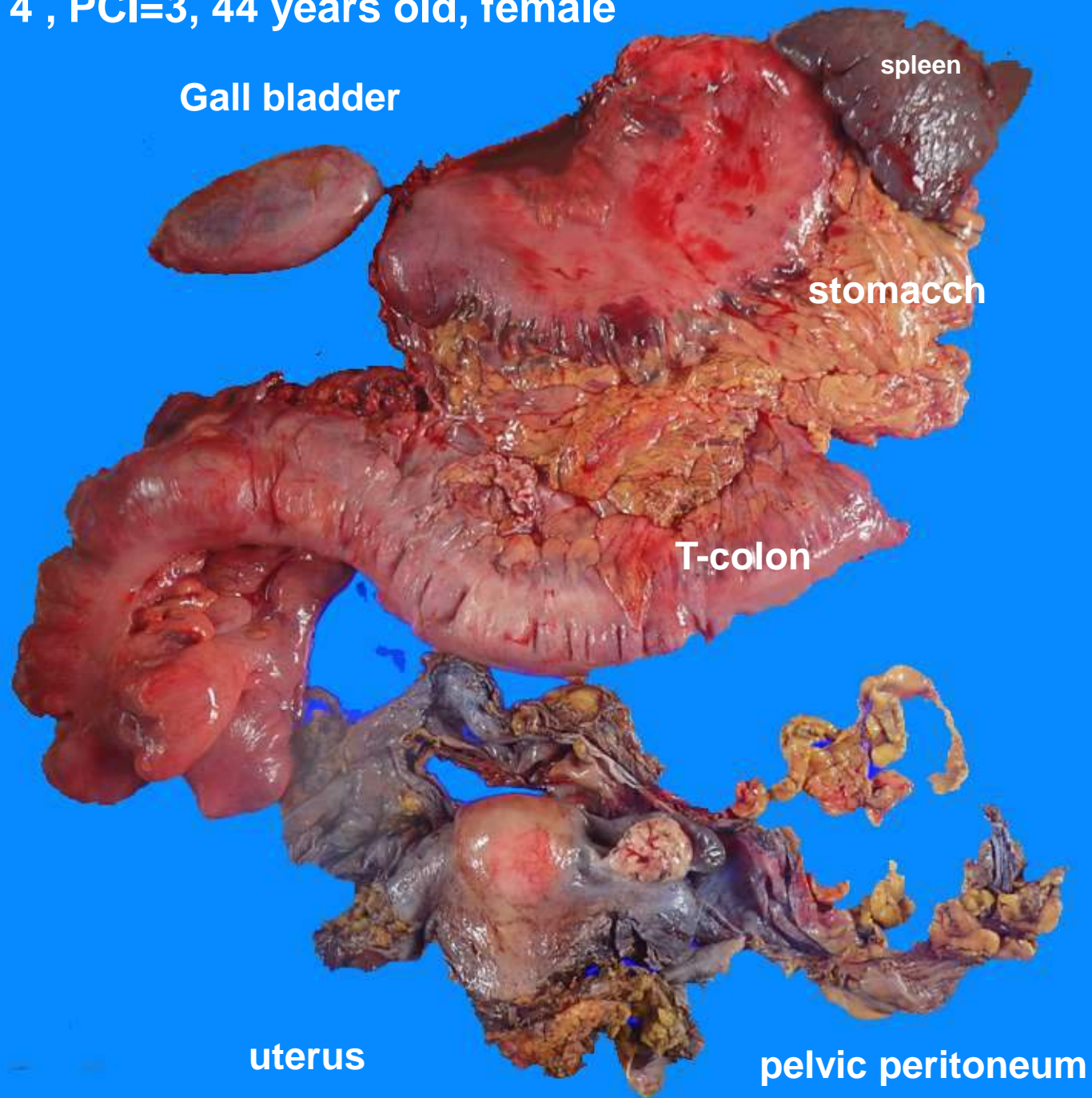


Peritonectomy for lower abdomen



日本腹膜播種学校・腹膜切除研修プログラム; 米村 豊 y.yonemura@coda.ocn.ne.jp まで
Peritonectomy training program: y.yonemura@coda.ocn.ne.jp

4 , PCI=3, 44 years old, female



Complete versus incomplete cytoreduction in peritoneal carcinosis from gastric cancer, with consideration to PCI cut-off. Systematic review and meta-analysis.

Coccolini F, Catena F, Glehen O, Yonemura Y, Sugarbaker PH, Piso P, Montori G, Ansaloni L.; PSOGI

MATERIAL AND METHODS:

A systematic review with meta-analysis of trials of complete vs incomplete cytoreduction in patients with peritoneal carcinosis from GC was performed.

RESULTS:

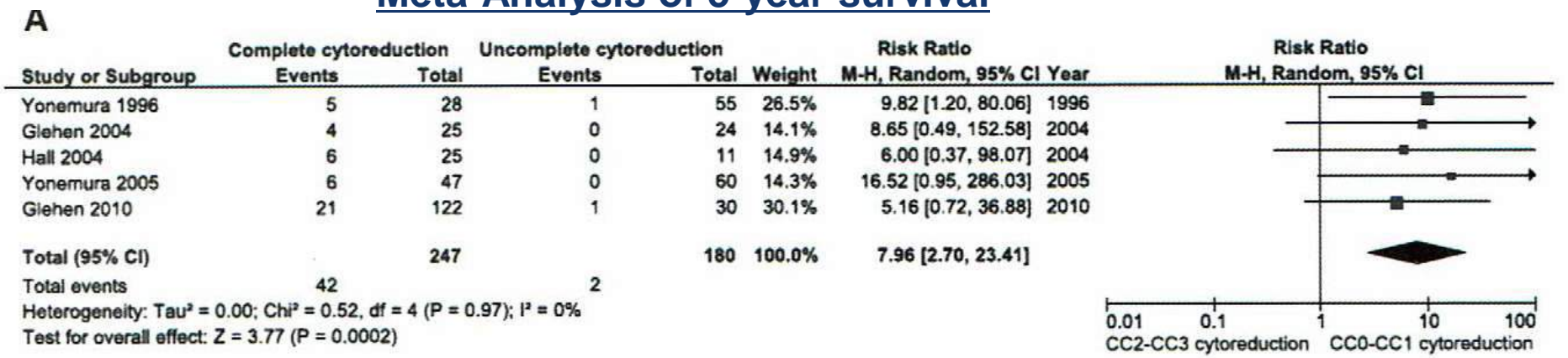
Nine trials have been included (748 patients: 417 with CCR-0 and 324 with CCR-1 cytoreduction). **5 years survival is favorable to CCR-0 (Risk Ratio: 8.0).**

CCR-0 vs. CCR-1 survival benefit was found above and below a PCI of 12.

CONCLUSIONS:

Overall survival is increased by CCR-0 cytoreduction in patients with PC from gastric origin

Meta-Analysis of 5-year survival



P1 patients treated with gastrectomy+chemotherapy

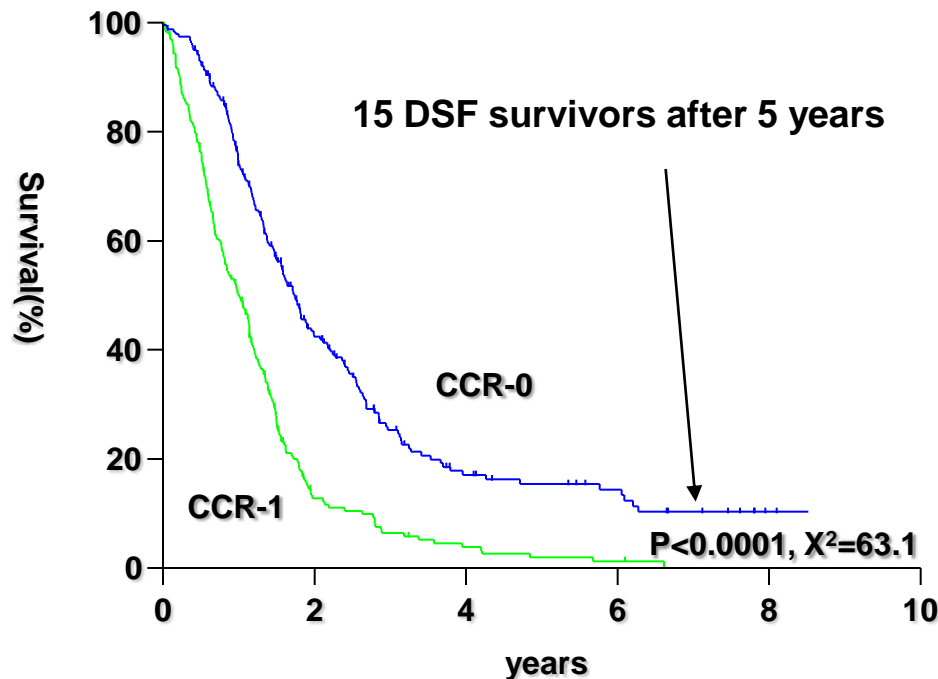
Authors	Treatments	Patients no.	MST	5-YSR	No. of DFS after 5 years
Ishigami H Gastric Ca. 2017;20:128	NIPS (S1+IP/IV PTX plus gastrectomy	53	30m	10%	0
Yang XJ Ann Surg oncol. 2011;18:1575	gastrectmy+HIPEC	27	12m	7%	1
Hong SH Gastric Ca.2013;16:290	gastrectomy+ Systemic chemo.	45	30m	8%	0
Total		126			1 (0.8%)

P1 patients treated with peritonectomy+chemotherapy

Glehen O Arch Surg. 2004;139:20	Peritonectomy+HIPEC	49	39m	13.00%	4
Hall JJ J Surg Oncol. 2012;105:43	Peritonectomy+HIPEC	34	11m	6%	1
Yonemura Y EJSO 2009;35:1158	Peritonectomy+NIPS+ HIPEC	275	16m	9%	9
Total		358			14 (4%)

Survival difference after complete and incomplete cytoreduction for PM from gastric cancer

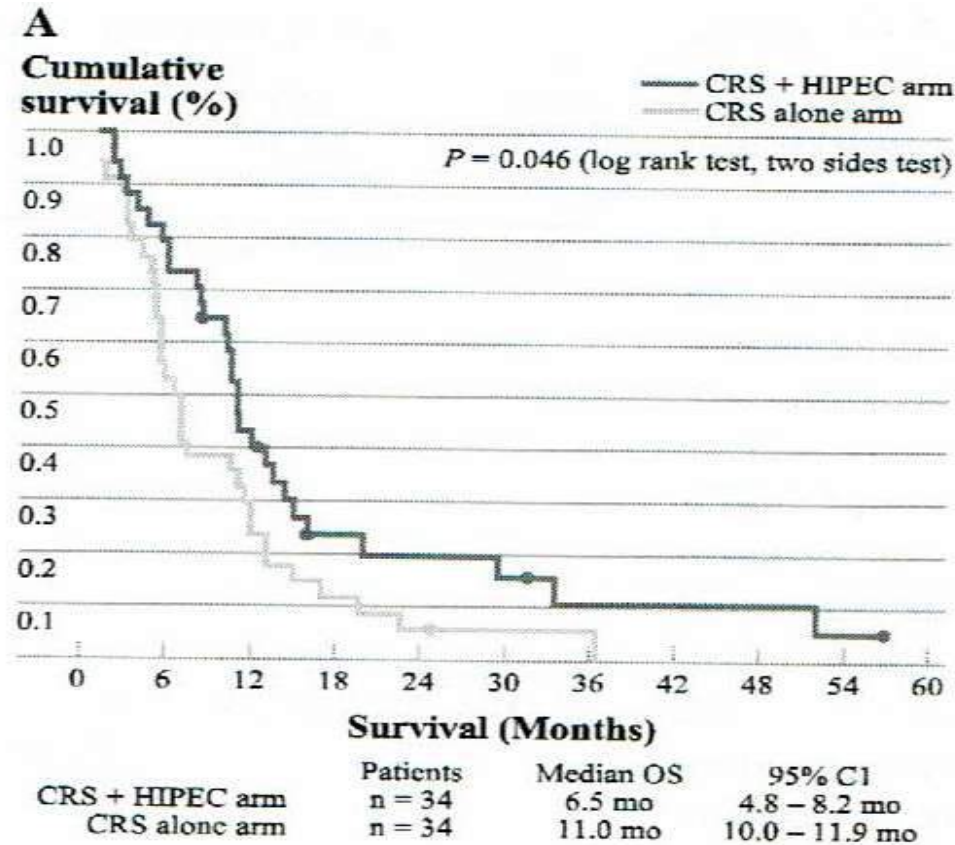
Survival curves of 472 patients with PM from gastric cancer.



Hyperthermic Intraperitoneal Chemo-perfusion (HIPEC)

RCT to study the effects on outcome after CRS+HIPEC vs. CRS in GC

Yan XJ: Ann Surg Oncol. 18:1575-1581,2011



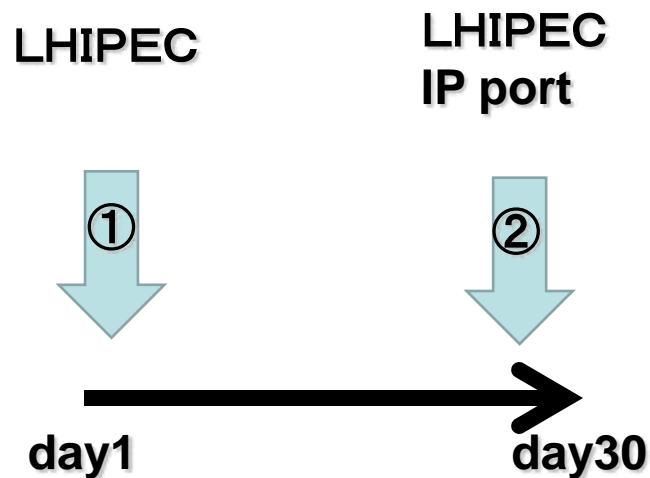
Prognostic factors=HIPEC, CC0, synchronous,

	MST	
CRS+HIPEC	11.0m	P=0.046
CRS alone	6.5m	

Prognostic factors=HIPEC, CC0, synchronous,

Direct effect on PM after one cycle of HIPEC

(gastric cancer with PM: N=53: *Yonemura Y: Ann Surg Oncol:24;478:2017*)



Mean PCI reduction: 2.4
from 14.2 ± 10.7 to 11.8 ± 11.0

Ascites reduction
from 840 ± 1695 to 303 ± 804 ml

Positive cytology became negative
13/19 (68%)

8 (15%) patients showed complete disappearance of PM



hyperthermic intraperitoneal chemotherapy (HIPEC)

5th International Workshop on Peritoneal Surface Malignancy in Milan (December 4-6, 2006)

J Surg Oncol. 2008 Sep 15;98(4):277-82. doi: 10.1002/jso.21054.

Consensus statement on the loco-regional treatment of appendiceal mucinous neoplasms with peritoneal dissemination (pseudomyxoma peritonei).

Moran B, Baratti D, Yan TD, Kusamura S, Deraco M.

Source

Colorectal Research Unit, North Hampshire Hospital, Basingstoke, Hampshire, UK.

Abstract

Pseudomyxoma peritonei (PMP) is a rare condition mostly originating from low malignant potential mucinous tumours of the appendix. Although this disease process is minimally invasive and rarely causes haematogenous or lymphatic metastases, expectation of long-term survival are limited with no prospect of cure. Recently, the combined approach of cytoreductive surgery (CRS) and perioperative loco-regional chemotherapy (PLC) has been proposed as the standard of treatment for the disease. The present paper summarizes the available literature data and the main features of the comprehensive loco-regional treatment of PMP. The controversial issues concerning the indications and technical methodology in PMP management were discussed through a web-based voting system by internationally known experts. Results

were presented for further evaluation during a dedicated session of **"The Fifth International Workshop held by PSOGI (Milan, Italy, December 4-6, 2006)".** The experts agreed that multiple prospective trials support a benefit of HIPEC in terms of improved survival.

Concerning the main controversial methodological questions, there was an high grade of consistency among the experts and agreement with the findings of the literature

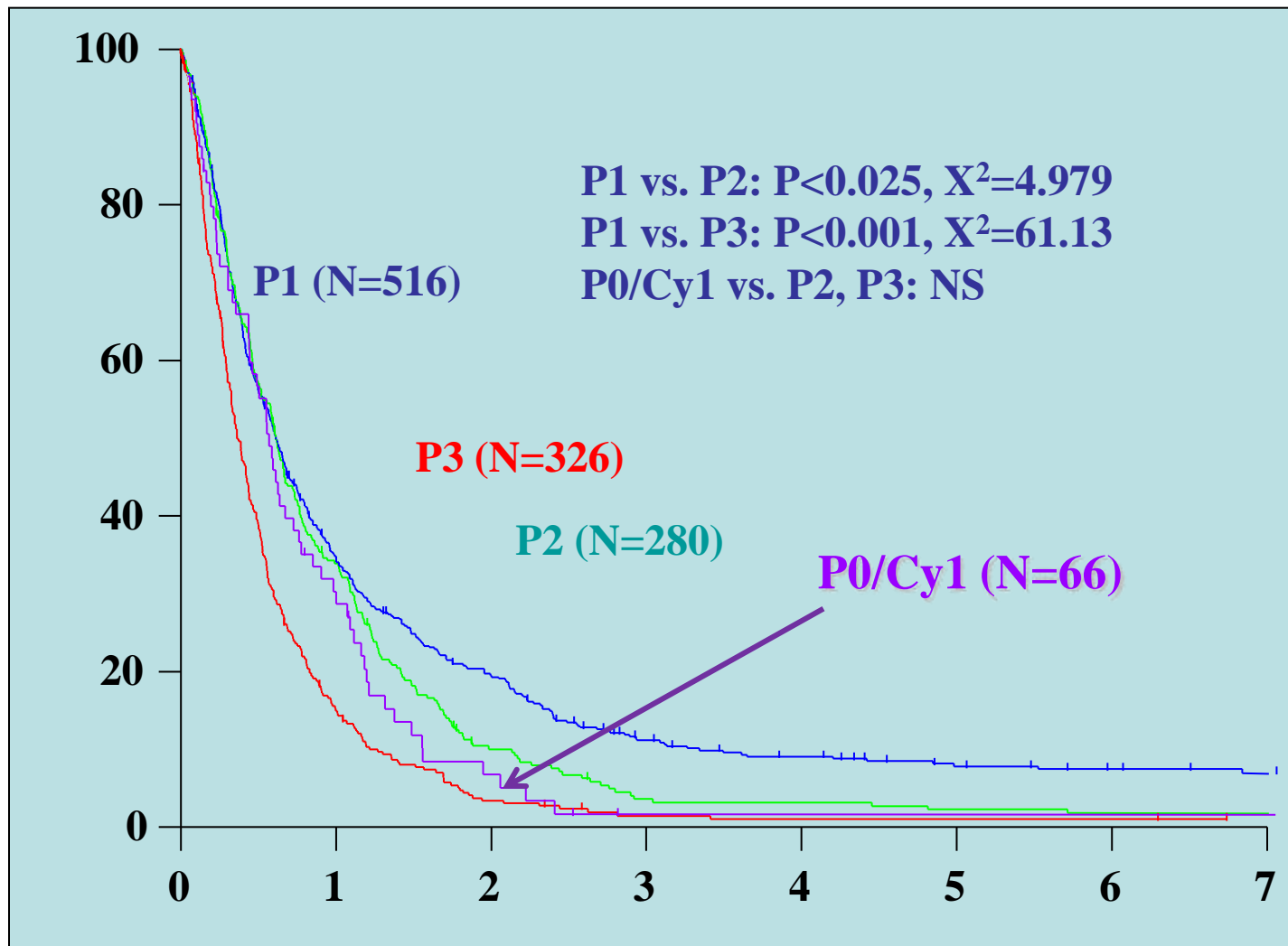
Concept of comprehensive treatment

**1: Complete removal of PM,
which cannot eradicate by Chemotherapy**

**2: Eradication of micrometastasis,
which can be eradicated by perioperative
chemotherapy**

Survival curves after CRS according to the P-grade.

Almost all P0CY1 patients must have residual micro metastasis even after curative gastrectomy



Outcome after radical gastrectomy

In P0CY1 patients

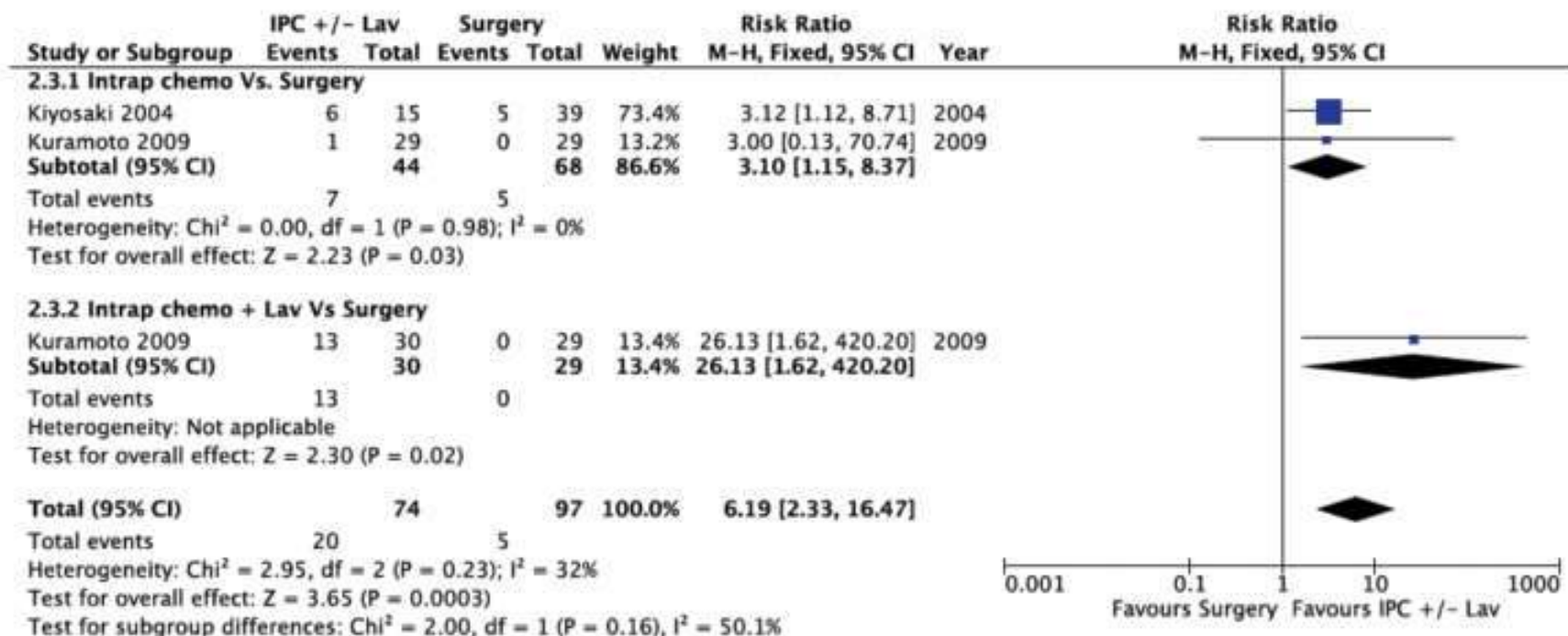
Authors	Treatments	Patients no.	MST	5-YSR	No. of DFS after 5 years
Ishigami H Gastric Ca. 2017;20:128	NIPS (S1+IP/IV PTX plus gastrectomy	11	37m	50%	4
Yonemura Y Glob J Gast Hepat 2014;2:1	NIPS (S1+DC)x 3 courses plus CRS plus HIPEC	20	36m	42%	2
Kuramoto M Ann Surg. 2009;250:246	EIPL+EPIC CDDP + gastrectomy	30	36m	44%	8
Imano M J Surg Oncol. 2012;105:43	EPIC, Gastrectomy+ IP PTX	10	38m	25%	2
Yonemura Y Cancer Ther. 2006;4:135.	gastrectomy+postoperative S1	35	37m	37%	4
Kodera Y EJSO 2009;35:1158	gastrectomy+postoperative S1	48	24m	32%	1
Total		154			21 (14%)

[Eur J Surg Oncol.](#) 2016 Sep;42(9):1261-7. doi: 10.1016/j.ejso.2016.03.035.
Epub 2016 Apr 19.

Effect of intraperitoneal chemotherapy and peritoneal lavage in positive peritoneal cytology in gastric cancer. Systematic review and meta-analysis.

[Coccolini F](#), [Catena F](#), [Glehen O](#), [Yonemura Y](#), [Sugarbaker PH](#), [Piso P](#),
[Ceresoli M](#), [Montori G](#), [Ansaloni L](#): PSOGI Group

Two- and five-years overall survival in patients with free cancer cells without carcinosis is incremented by intraperitoneal chemotherapy.



Concept of comprehensive treatment

**1: Complete removal of macroscopic PM,
which cannot eradicate by Chemotherapy**

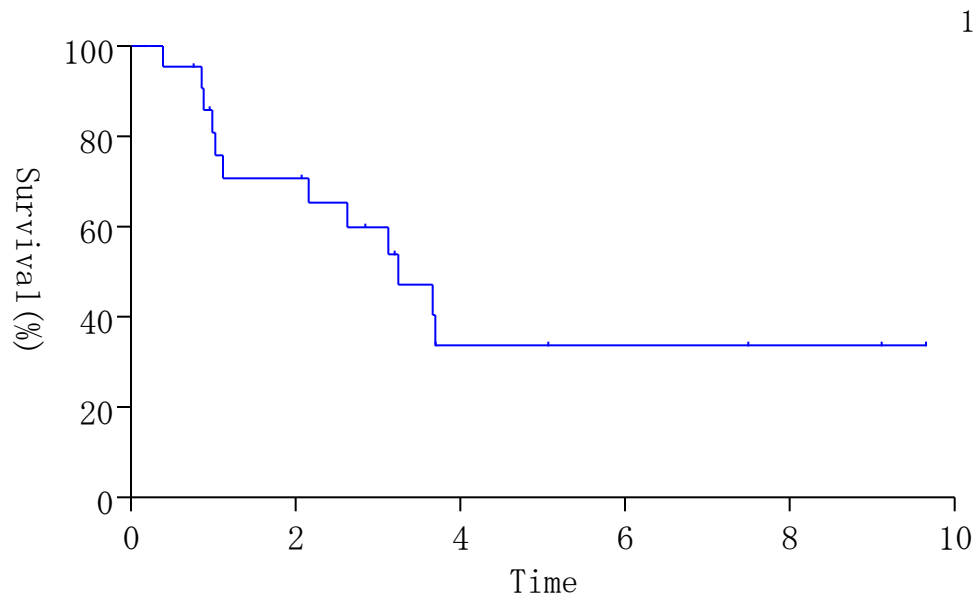
2: Eradication of micrometastasis,

**Micrometastasis can be completely
eradicated around 20-30% of P0Cy1 patients.**



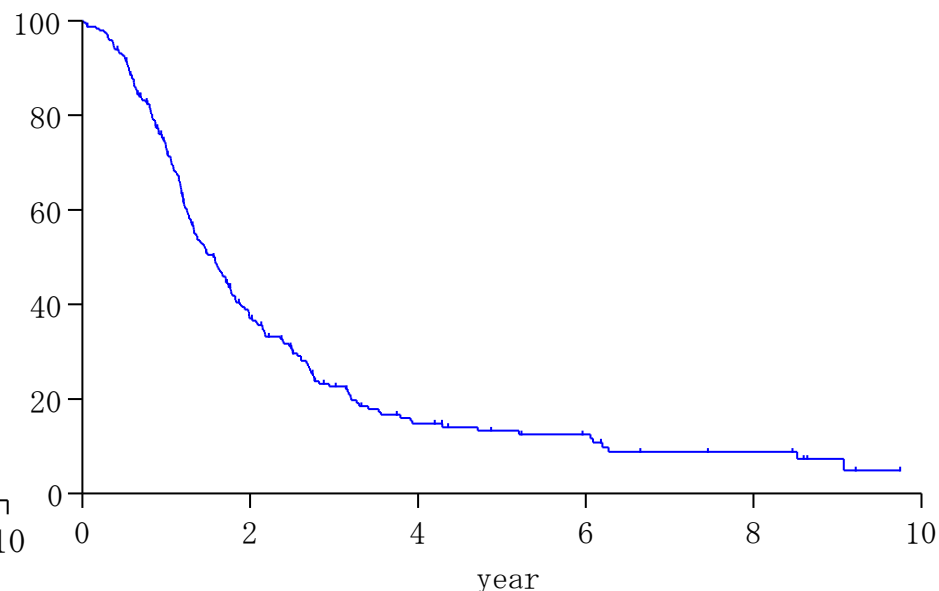
**Cure can be obtained
in selected patients with PM**

Survival curves of 23 P0/CY1 patients underwent CCR-0



MST: 38.4 m
5 yrsr: 33.7%
Disease free survivors after 5 years: 5

Survival curves of 170 P1 patients underwent CCR-0



MST: 19.2 m
5 yrsr: 13.2%
Disease free survivors after 5 years: 9

**Cure or recurrence may depend on
the residual tumor burden,
chemo-sensitivity used**



**Consecutive treatment using
NIPS, HIPEC, EIPL, EPIC
and postoperative chemotherapy
for the same patients
may improve the outcome**

Selection of POC according to the oncological aspects of view in each patients. Options should be changed

1: Diagnosis of PM: Exploratory Lap. and Laparoscopic HIPEC

2: Neoadjuvant chemotherapy

3: Extensive Intraperitoneal lavage (EIPL)

4: Cytoreductive Surgery (Peritonectomy)

5: HIPEC

6: Early postoperative IP chemotherapy (EPIC)

7: Late postoperative systemic chemotherapy

Highly malignant tumor: GC/CRC/pancreas/Biliary

1+2+3+4+5+6+7

Intermediate tumor: Ovarian Ca/Mesothelioma

1+2+3+4+5+7

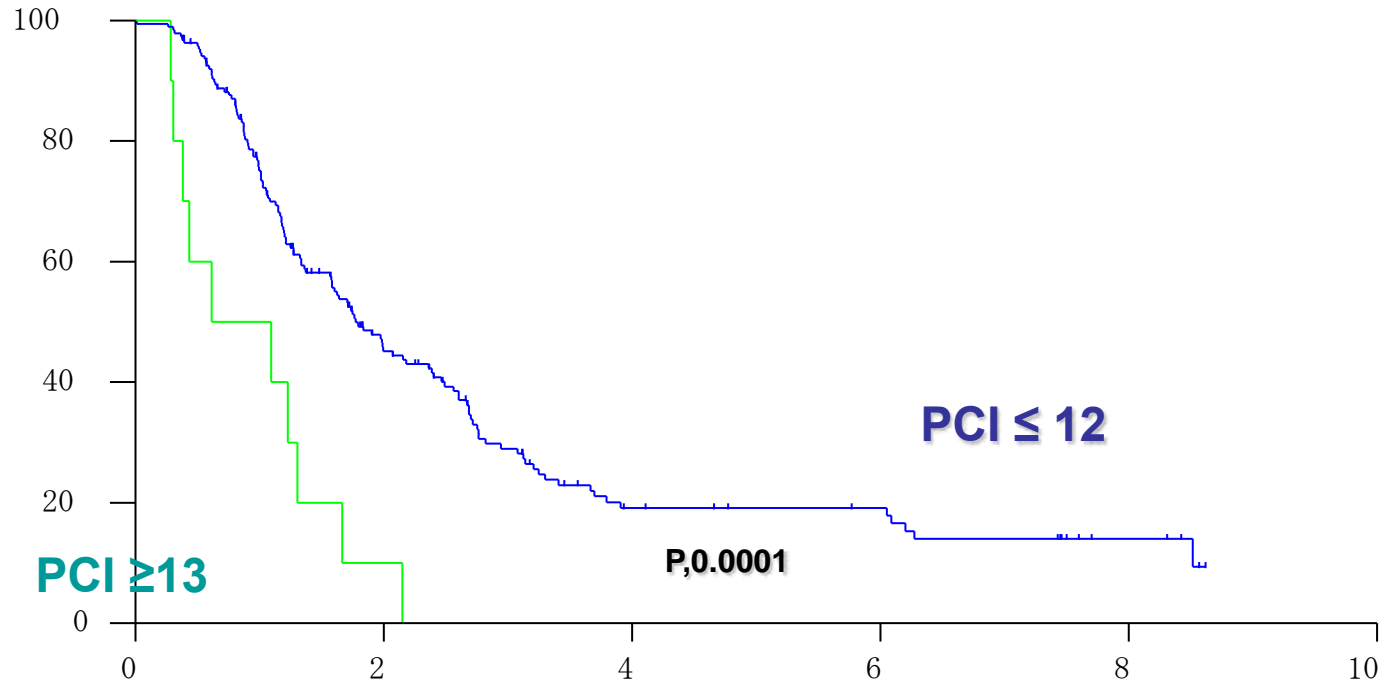
Low malignant tumor:

3+4+5

Survival according to PCI-cutoff value

PCI cut-off value is the most significant PCI level for the favorable prognosis after comprehensive treatment

Gastric cancer



Eur J Surg Oncol. 2015 41(7):911-9. Coccolini F,
Catena F, Glehen O, Yonemura Y, Sugarbaker PH, Piso
P, Montori G, Ansaloni L.; PSOGI

Selection of patients for comprehensive treatment

Candidates should be selected by TM, CT, MRI, Lap and PET during NAC

Selection criteria for CRS in patients with PM

- 1. Patients who undergo complete cytoreduction**
- 2. PCI after NAC \leq cut-off level**
- 3. Small bowel PCI \leq cut-off level, with a minimum of 200cm of uninvolved small bowel**
- 4. Responders of NAC**