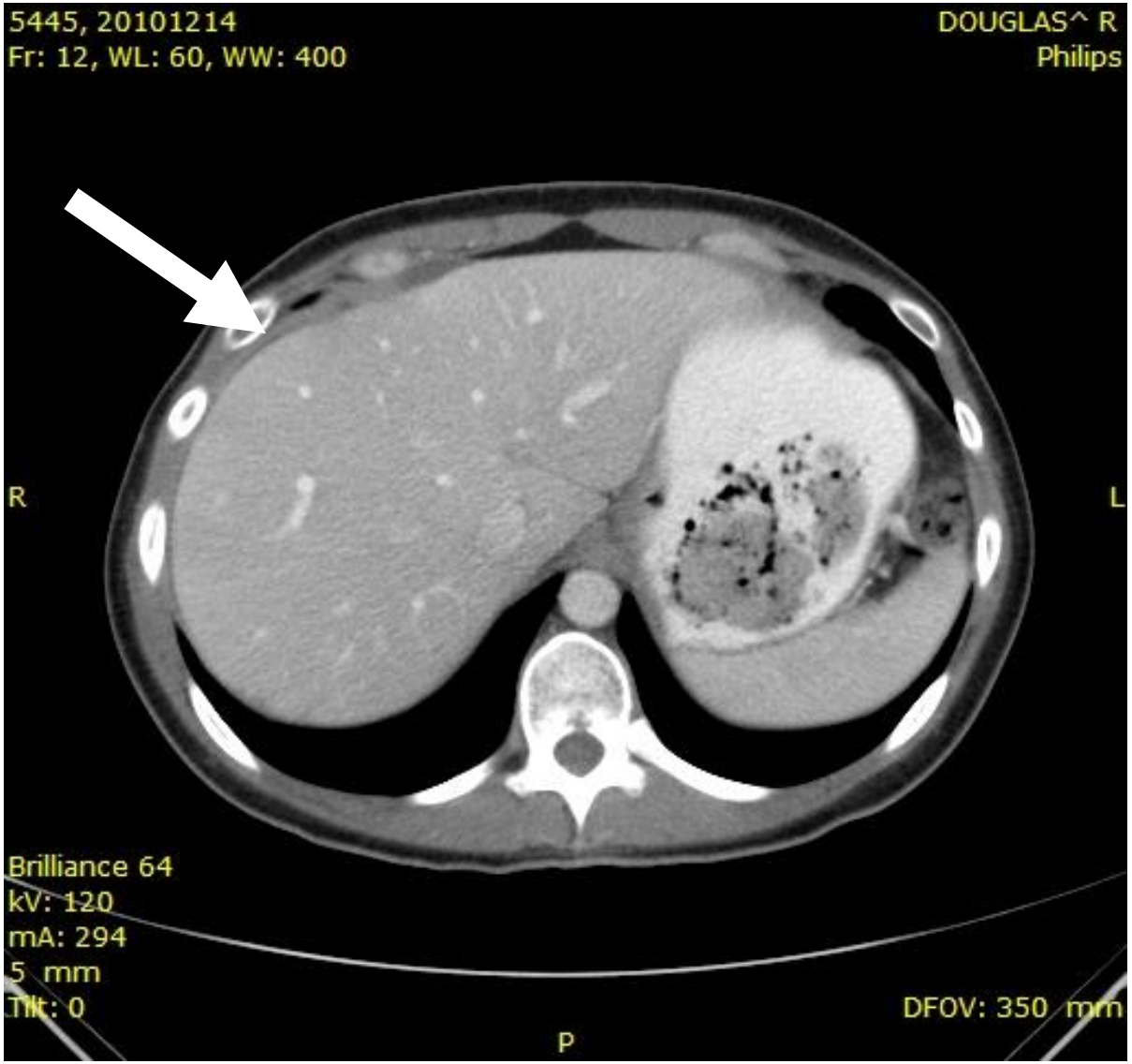
Patient Presentation

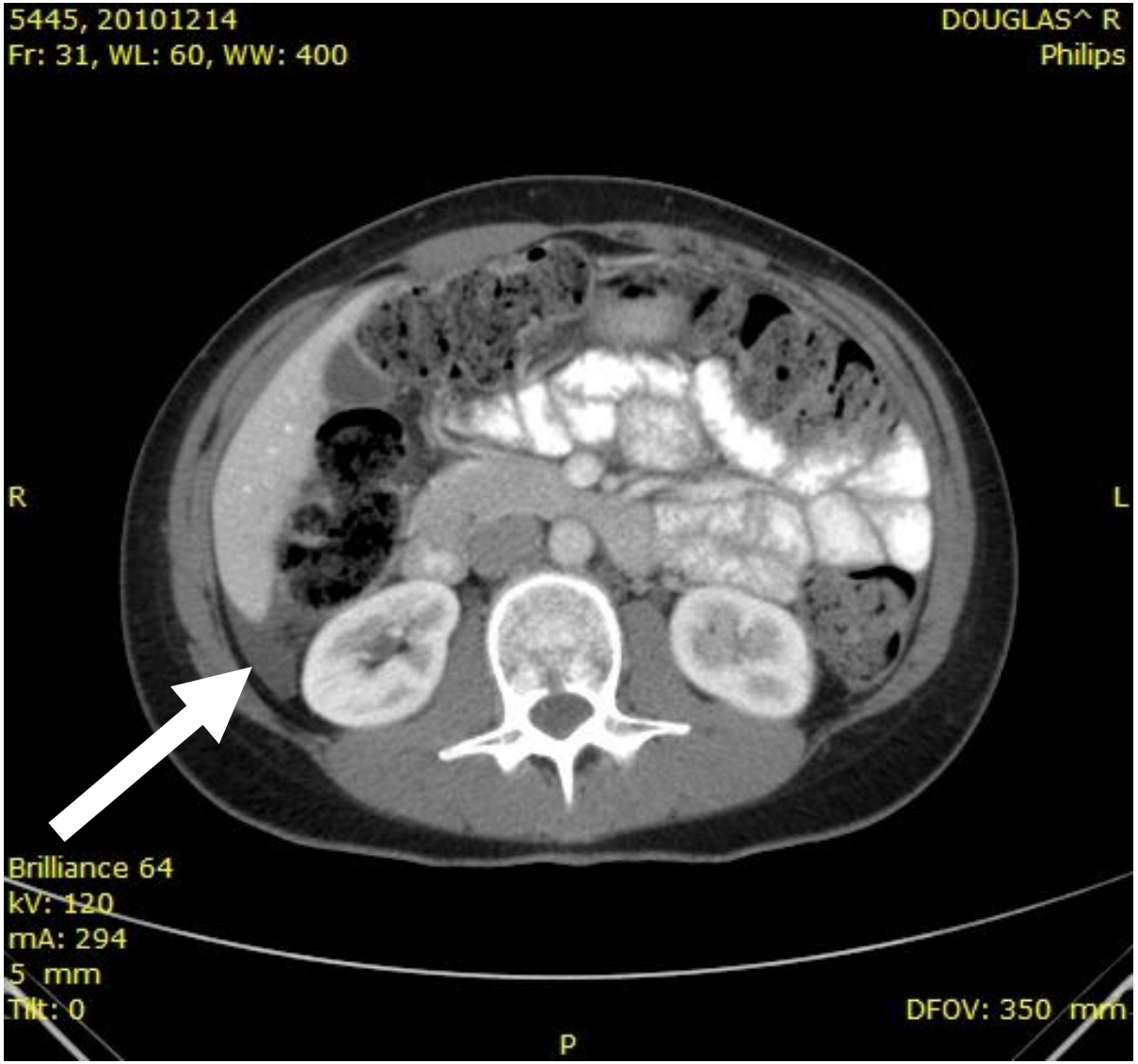
32 y.o. female complains of lower abdominal mass

CEA = 433, CA125 = 201

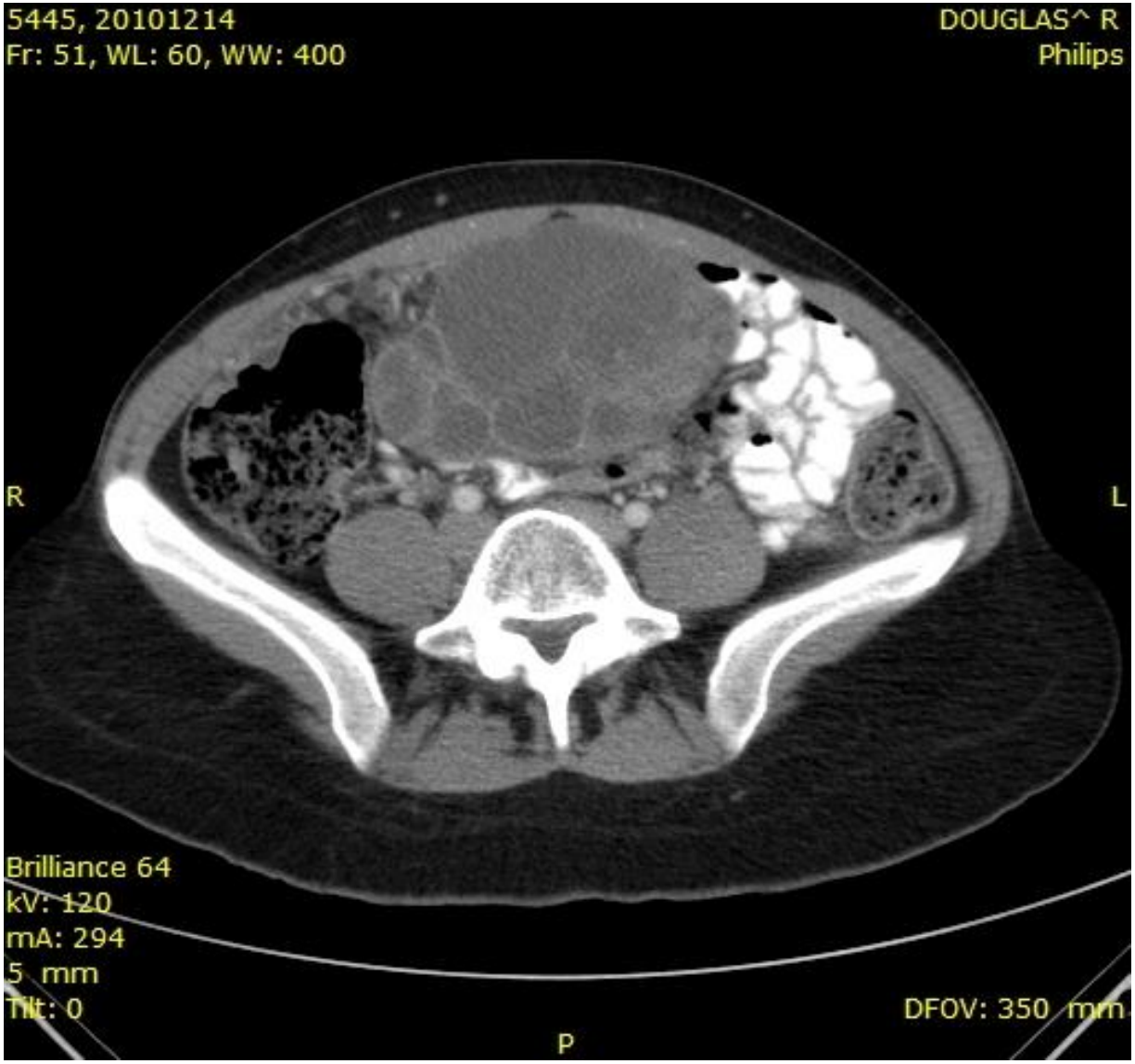
CT shows: Thickening of the right hemidiaphragm



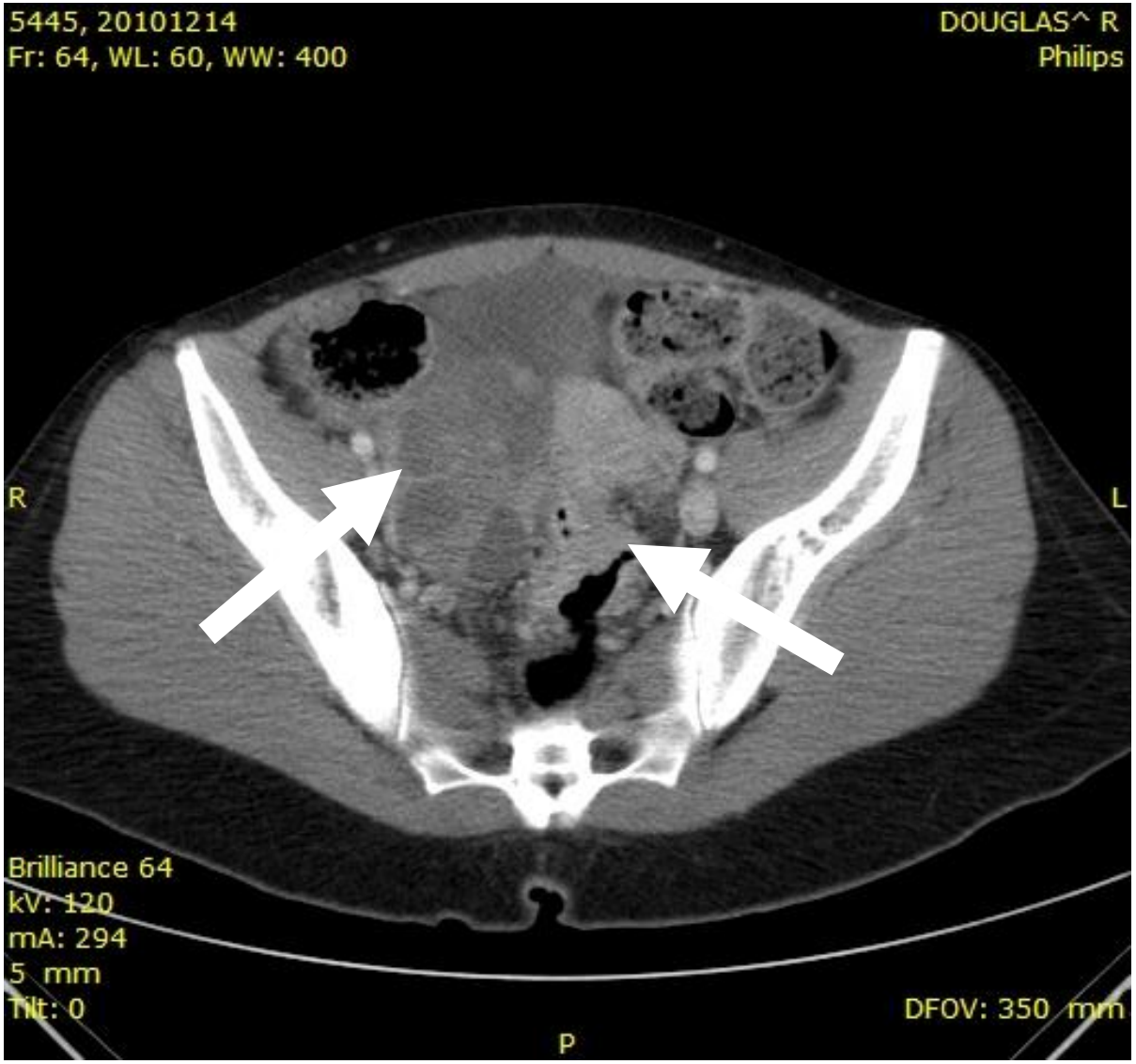
CT shows: Fluid in the right paracolic sulcus



CT shows: Large multicystic left ovarian mass



CT shows: Large multicystic right ovarian mass and obstructing rectal cancer



1/11/2011 Surgical procedures

- Exploratory laparotomy
- Greater and lesser omentectomy
- Right upper quadrant peritonectomy
- Pelvic peritonectomy
- Hysterectomy and bilateral salpingo-oophorectomy
- Right colectomy
- Low anterior resection with anastomosis
- HIPEC plus 5-FU
- Diverting ileostomy

- PCI = 20
- CC score = 0
- Hospital stay = 19 days
- Pathology = $T_4N_1M_1$ mid-rectal cancer
- EPIC 5-FU for 4 days
- Plan: Complete FOLFOX then close ileostomy with a second-look surgery

Original assigned title:
Surgical debulking and hyperthermic chemotherapy for metastatic colon cancer: If you select the right patients, long term survival can be achieved.

Revised title:
Cytoreductive surgery and perioperative chemotherapy for metastatic colon cancer to peritoneal surfaces: If you select the right patients, long term survival can be achieved.

Paul H. Sugarbaker, MD, FACS, FRCS

Washington Cancer Institute

Washington, DC, USA

Definitions:

- **Cytoreduction –** removal of abdominal and pelvic malignancy to the cellular level of residual disease. It is combined with perioperative intraperitoneal hyperthermic and/or normothermic chemotherapy. It has curative intent.
- **Debulking –** removal of gross disease with no attempt to make the patient visibly disease-free in the abdomen and pelvis. Used before or after systemic chemotherapy. It has palliative intent.

Cytoreduction

Visceral Resections

- Prior abdominal incisions
- Greater and lesser omentum +/- spleen
- Rectosigmoid colon
- Uterus and ovaries
- Gall bladder

Peritonectomy Procedures

- Anterior parietal peritonectomy
- Left upper quadrant peritonectomy
- Right upper quadrant peritonectomy
- Pelvic peritonectomy
- Lesser omentectomy with stripping of the omental bursa

Perioperative chemotherapy:

- HIPEC – hyperthermic intraperitoneal chemotherapy
- HIPEC + 5-FU
- EPIC – early postoperative intraperitoneal chemotherapy

Washington Hospital Center/Washington Cancer Institute
Intraoperative Surgical Oncology Bidirectional Chemotherapy Orders

Pseudomyxoma peritonei, adenocarcinoma from the appendix, colon, or rectum

a) Add mitomycin C _____mg to 2 liters of 1.5% dextrose peritoneal dialysis solution.

b) Add doxorubicin _____mg to the same 2 liters of 1.5% dextrose peritoneal dialysis solution.

c) Dose of mitomycin C and doxorubicin is 15 mg/m² for each chemotherapy agent.

d) Add fluorouracil (400 - 800 mg/m²) _____ mg and leucovorin _____ mg (20 mg/m²) to separate bags of 250 ml 0.9% sodium chloride. Begin infusion IV over 7 - 10 minutes of both drugs simultaneously with IP chemotherapy.

e) Send all the above to operating room #_____ at _____o'clock on _____ (Date) for a 90-minute treatment.

Washington Hospital Center/Washington Cancer Institute

Early Postoperative Surgical Oncology Intraperitoneal Chemotherapy Orders

FLUOROURACIL Post–op Days 1-4:

a) Fluorouracil _____ mg (400 mg/m² for females and 600 mg/m² for males, maximum dose: 1400 mg) and 50 meq sodium bicarbonate in _____ml 1.5% Dianeal via the Tenckhoff catheter or IP port daily: Start date:_____ Stop date: _____

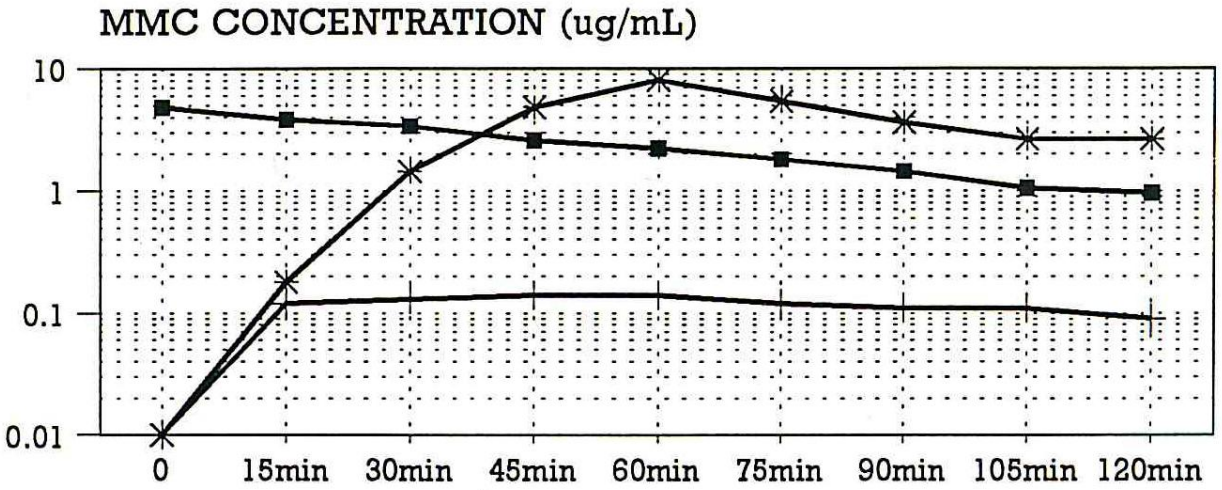
b) Instill as rapidly as possible via the Tenckhoff catheter or IP port. Dwell for 23 hours. Drain by Jackson-Pratt drains for one hour prior to the next instillation.

c) Continue to drain the abdominal cavity by Jackson-Pratt drains after the last dose of IP chemotherapy.

d) During the initial 6 hours after chemotherapy instillation, patient's bed should be kept flat. The patient should be on the right side during instillation. Turn ½-hour post instillation onto the left side and continue to change sides at ½-hour intervals for 6 hours.

e) Monitor with a pulse oximeter during the first 6 hours of each IP chemotherapy.

Pharmacology of intraperitoneal mitomycin C



Perfusate conc.	4.8	3.84	3.36	2.58	2.22	1.8	1.44	1.05	0.96
Plasma conc.	0	0.12	0.13	0.14	0.14	0.12	0.11	0.11	0.09
Urine conc.	0	0.18	1.44	4.8	8.04	5.4	3.6	2.64	2.64
Urine vol.(mL)	0	150	150	25	50	60	75	125	100
MMC excreted(ug)	0	27	216	120	402	324	270	330	264

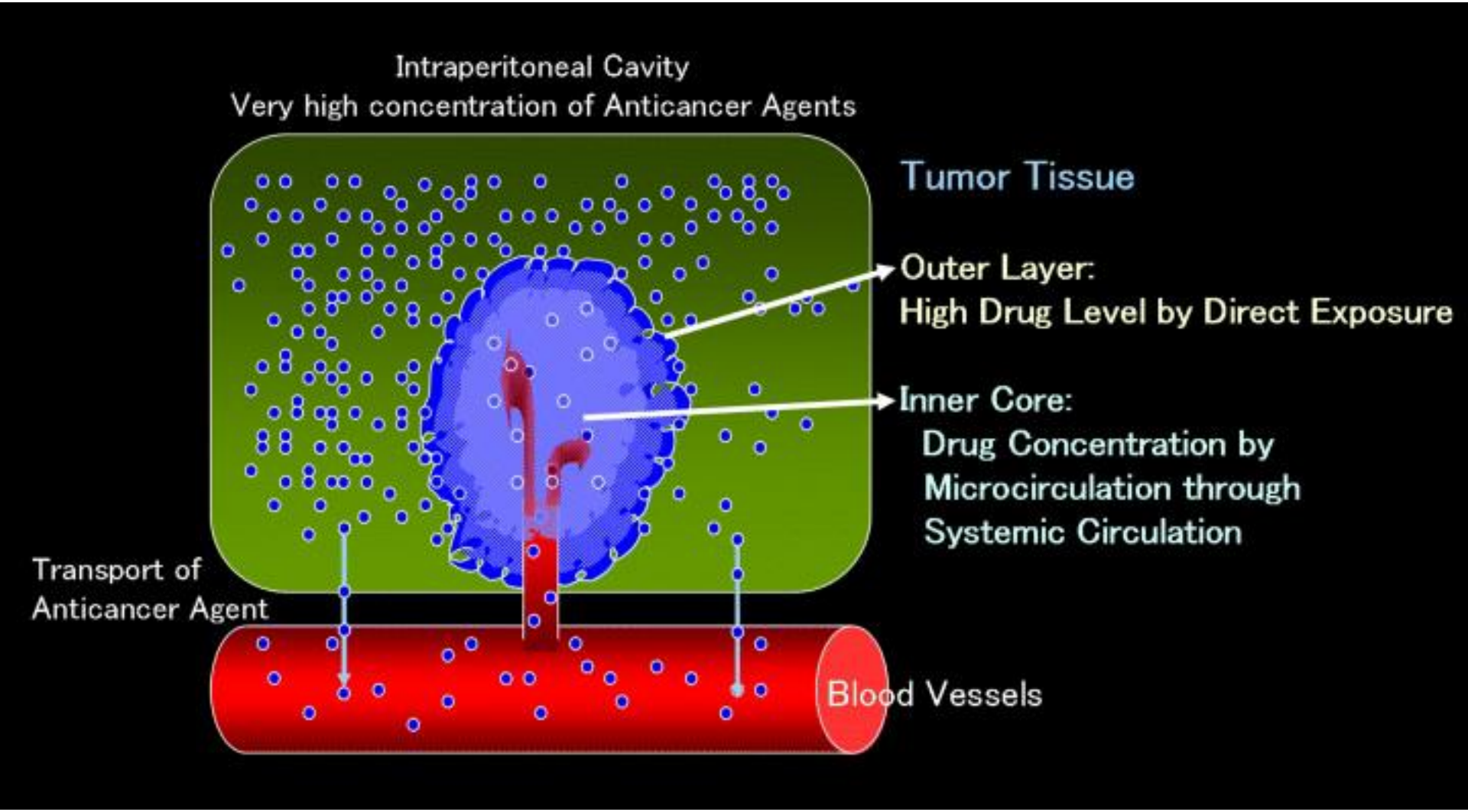
SAMPLE TIME(MINS)

LEVELS

Perfusate conc. Plasma conc. Urine conc.

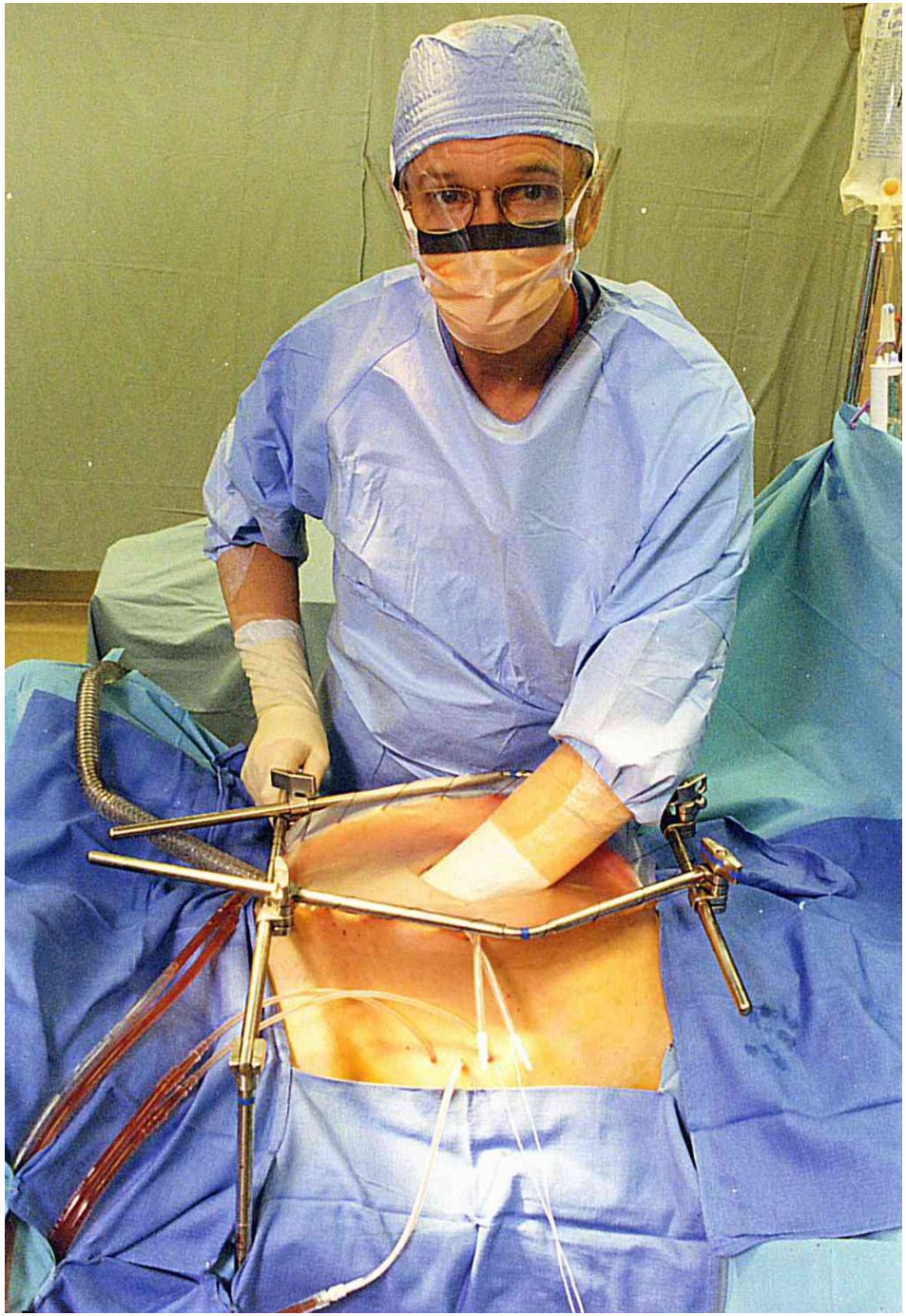
MMC DOSE = 15mg in 3L Dianeal
TOTAL MMC ABSORBED = 12mg(80% of dose)
TOTAL MMC EXCRETED = 2mg(13% of dose)

Bidirectional chemotherapy (intraperitoneal and intravenous)

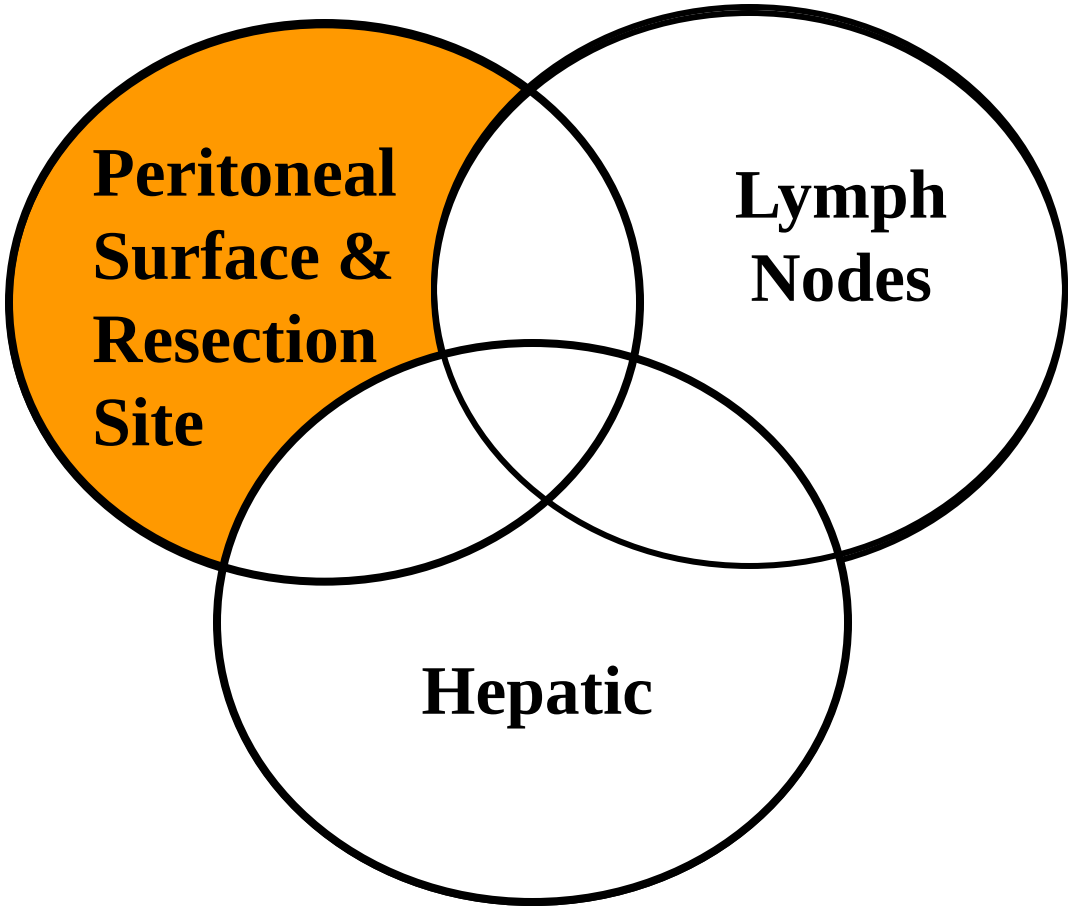


HIPEC-5FU introduced by Elias and widely used in Europe

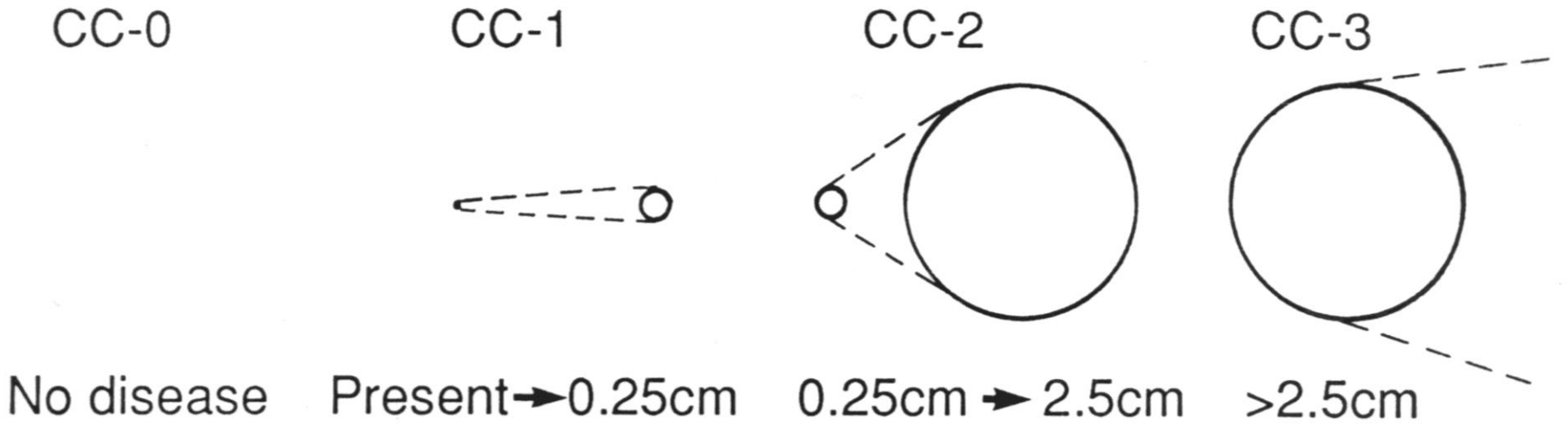
1. 5-FU 400 mg/m^2 and leucovorin 20 mg/m^2 1 hour prior to administration of IP chemotherapy.
2. Oxaliplatin 300 mg/m^2 and irinotecan 200 mg/m^2 in 2 L/m^2 5% dextrose.
3. Lavage at 43 C for 30 minutes.



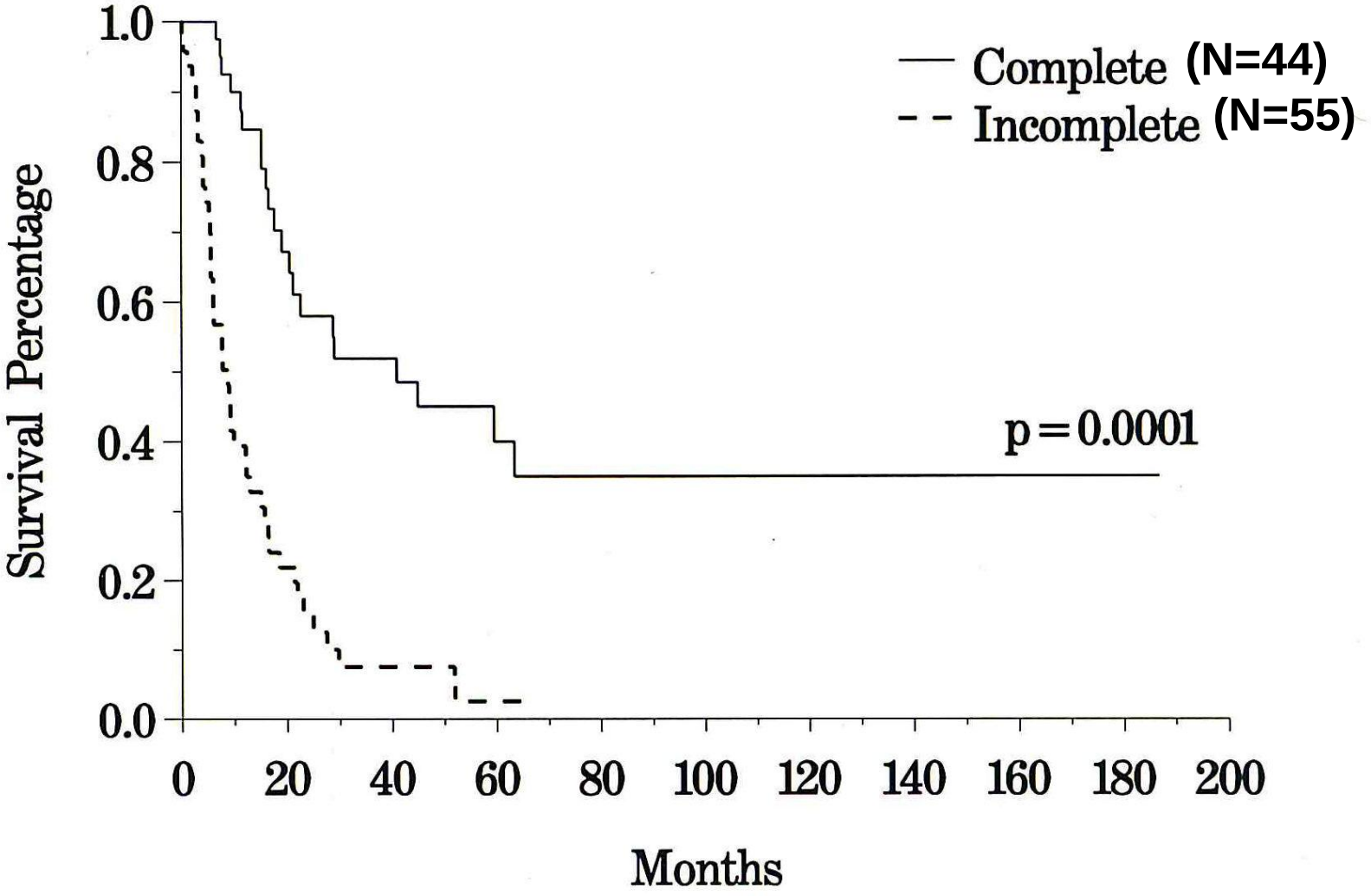
Sites of treatment failure for large bowel cancer



Completeness of cytoreduction assessment is performed after the maximal surgical effort has been completed

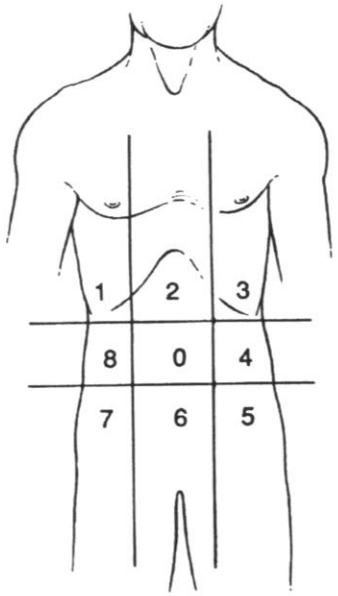


Survival of All Colon Cancer Patients by Completeness of Cytoreduction



Pestieau SR and Sugarbaker PH. Dis Colon Rectum, 2000

Peritoneal cancer index (PCI) is determined after the abdominal exploration is complete. It assists in making a surgical judgment to proceed or not with an attempt at complete cytoreduction.

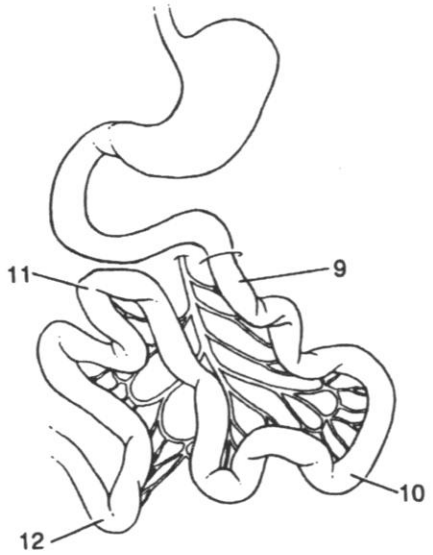


Regions	Lesion Size
0 Central	____
1 Right Upper	____
2 Epigastrium	____
3 Left Upper	____
4 Left Flank	____
5 Left Lower	____
6 Pelvis	____
7 Right Lower	____
8 Right Flank	____
9 Upper Jejunum	____
10 Lower Jejunum	____
11 Upper Ileum	____
12 Lower Ileum	____

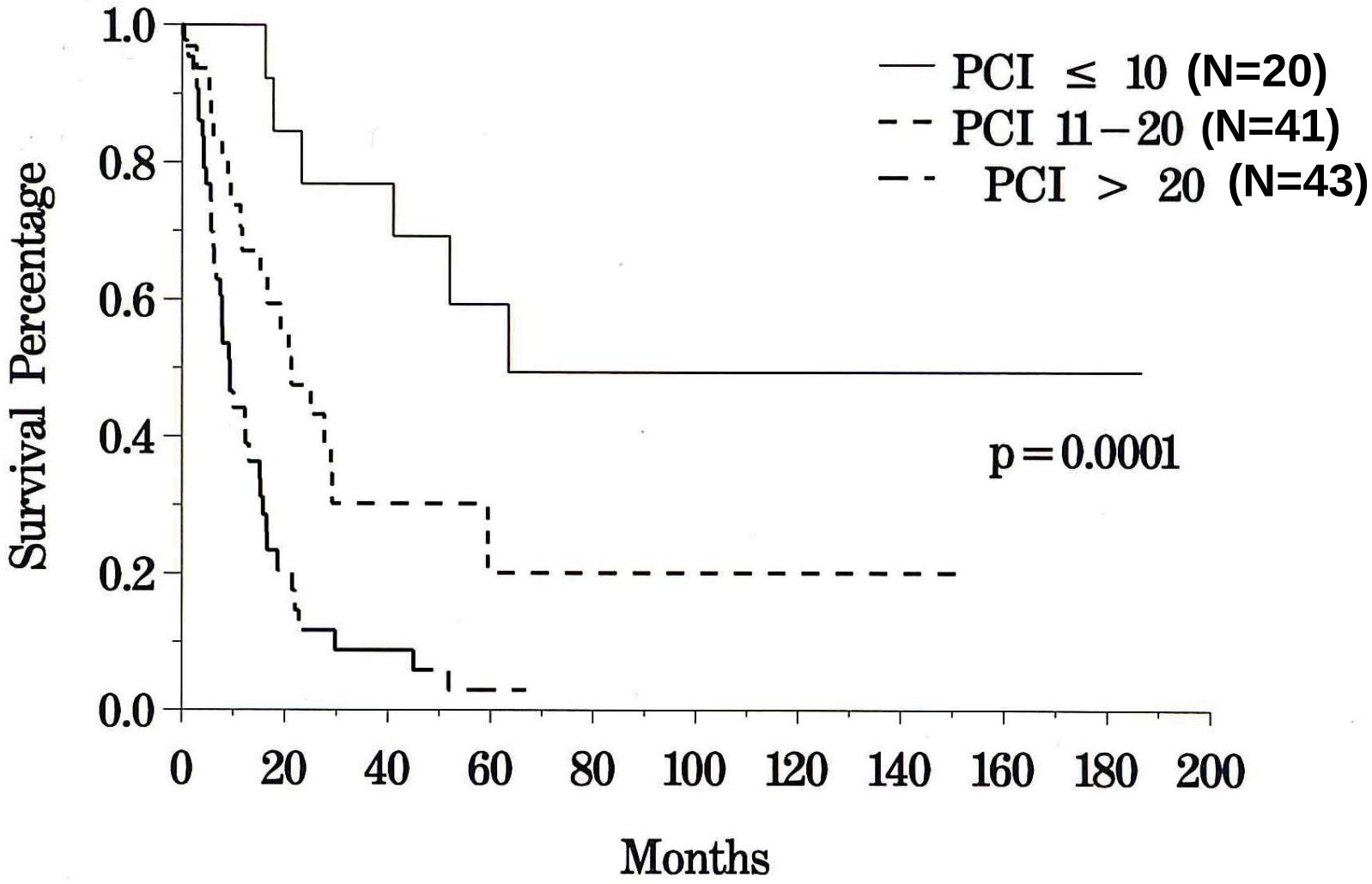
PCI ☐

Lesion Size Score

LS 0 No tumor seen
LS 1 Tumor up to 0.5 cm
LS 2 Tumor up to 5.0 cm
LS 3 Tumor > 5.0 cm or confluence



Survival of All Colon Cancer Patients by PCI groups



Pestieau SR and Sugarbaker PH. Dis Colon Rectum, 2000

Multivariate Analysis of Prognostic Factors for Overall Survival of 523 Patients Treated With Cytoreductive Surgery Combined With Perioperative Intraperitoneal Chemotherapy

Variable	Multivariate Analysis		
	P	Hazard Ratio	95% CI
Peritoneal cancer index*	< .001	1.052	1.029 to 1.076
Completeness of surgery†	.07	1.398	0.970 to 2.014
Positive lymph nodes‡	.02	1.534	1.058 to 2.224
Adjuvant chemotherapy‡	.002	0.578	0.407 to 0.820

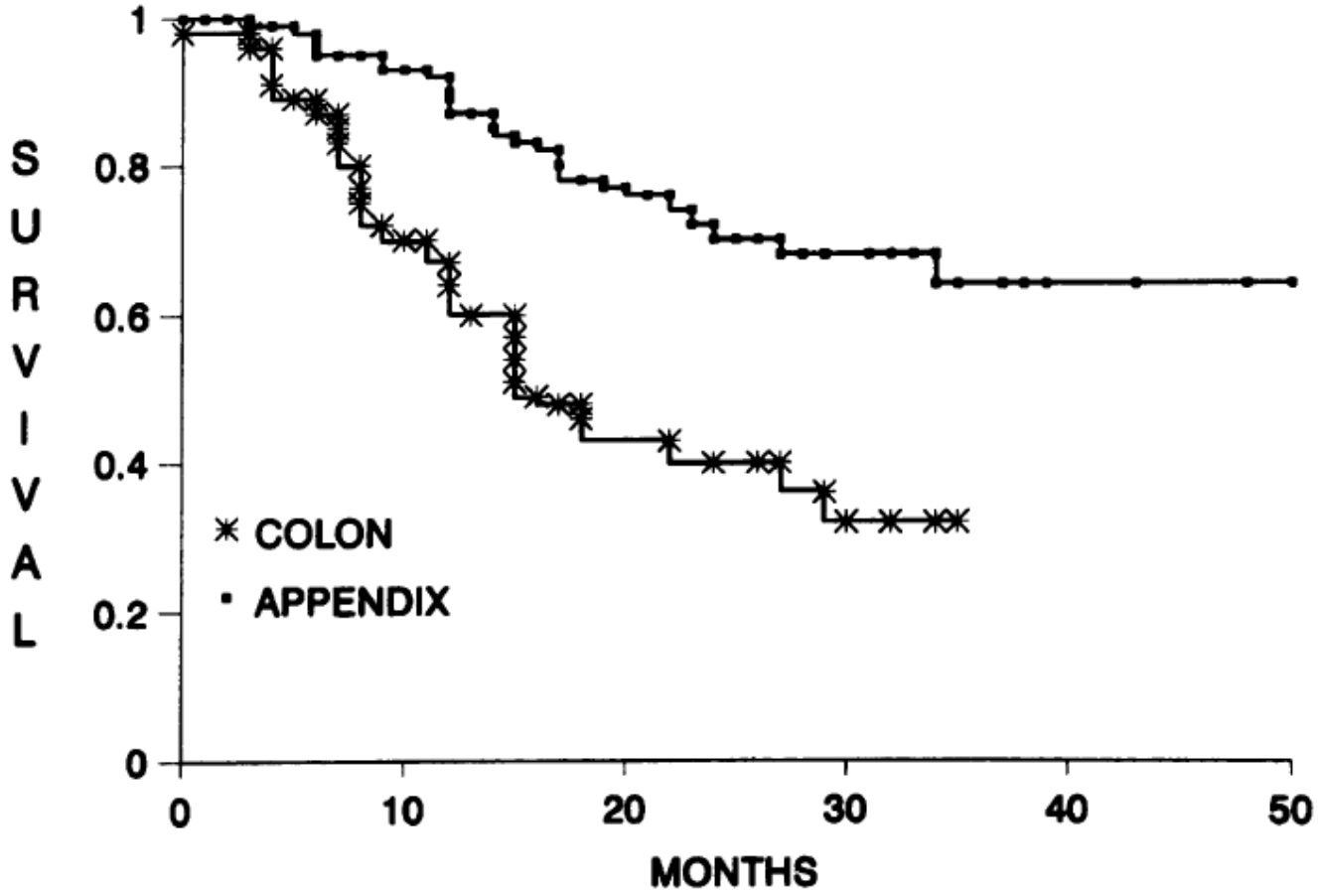
*For each additional point in the peritoneal cancer index, the risk of death of the relative risk increases (ie, by 5.2%).

†Completeness was divided into three categories: completeness of the cancer resection (CCR)-0, CCR-1, and CCR-2. Passing from one category to another increases the risk of death by 39%.

‡Compared in two classes (ie, yes or no).

Elias D, et al. JCO, Jan. 2010

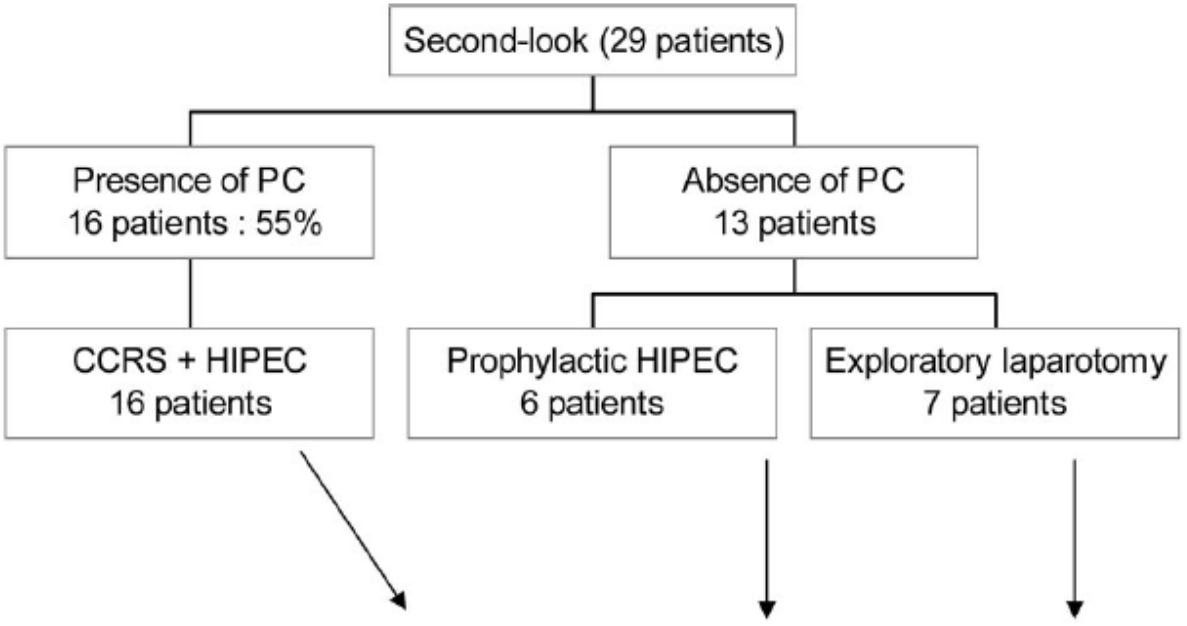
Carcinomatosis from colon cancer vs. appendix



Survival of patients with appendix cancer vs. colon cancer. P=0.0001)

Sugarbaker PH, Jablonski KA. Ann Surg, 1995

Results of second-look surgery to detect early peritoneal carcinomatosis in high-risk patients.



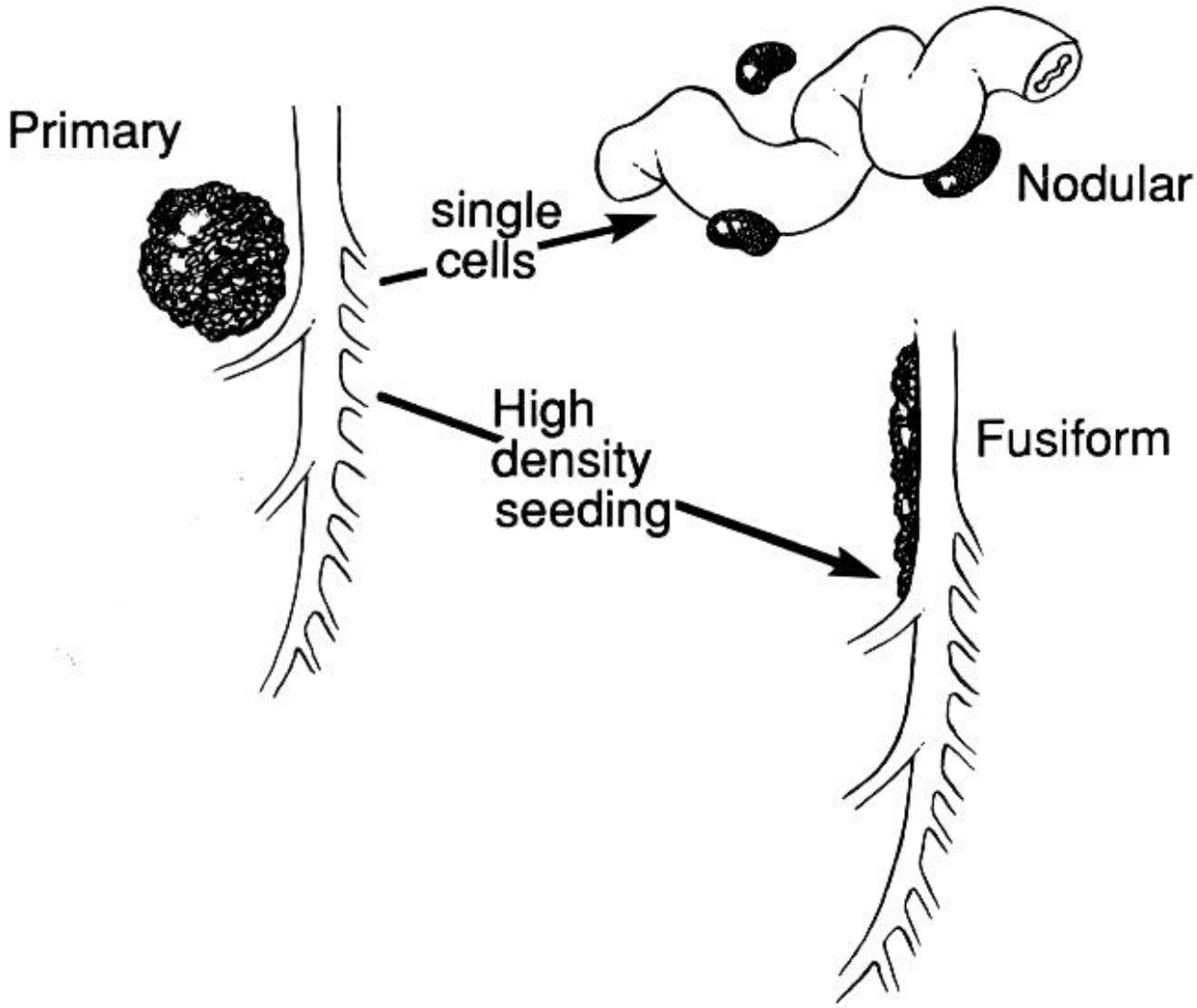
- *Free of disease*:	8	5	4
- *PC at relapse*:	4	0	3
- *Isolated visceral metastases*:	4	1	0

PC: Peritoneal Carcinomatosis,

CCRS: Complete cytoreductive surgery; HIPEC: Hyperthermic peritoneal chemotherapy

Elias D, et al. Ann Surg, 2010

Gastrointestinal Cancer Progression – similar mechanisms for carcinomatosis and local recurrence



Patients with colorectal cancer recommended for cytoreductive surgery and perioperative chemotherapy

Positive peritoneal cytology
Ovarian involvement
Peritoneal seeding on the serosal surface of the primary tumor
Rupture of a necrotic tumor mass
Adjacent organ involvement
Intraoperative tumor spill
Perforation of the primary tumor
Limited peritoneal seeding with a peritoneal cancer index of <20
Limited peritoneal seeding so that complete cytoreduction can be achieved

Sugarbaker PH. Successful management of microscopic residual disease in large bowel cancer. Cancer Chemother Pharmacol, 1999.

Evidence-Based Medicine Regarding Management of Carcinomatosis from COLORECTAL CANCER

Systemic Chemotherapy

Five-year data and prognostic factor analysis of oxaliplatin and irinotecan combinations for advanced colorectal cancer (N9741) – Sanoff et al. JCO, Dec. 2008

Median survival 20.2 months with 5% 5-year survival

Data on the objective response and survival not available for the subset of patients with carcinomatosis

CRS + HIPEC

Phase III study – Verwaal et al. JCO, 2003

Multiinstitutional registry – Glehen et al. JCO, 2004 (N=506)

Systematic review – Yan et al. JCO, 2006

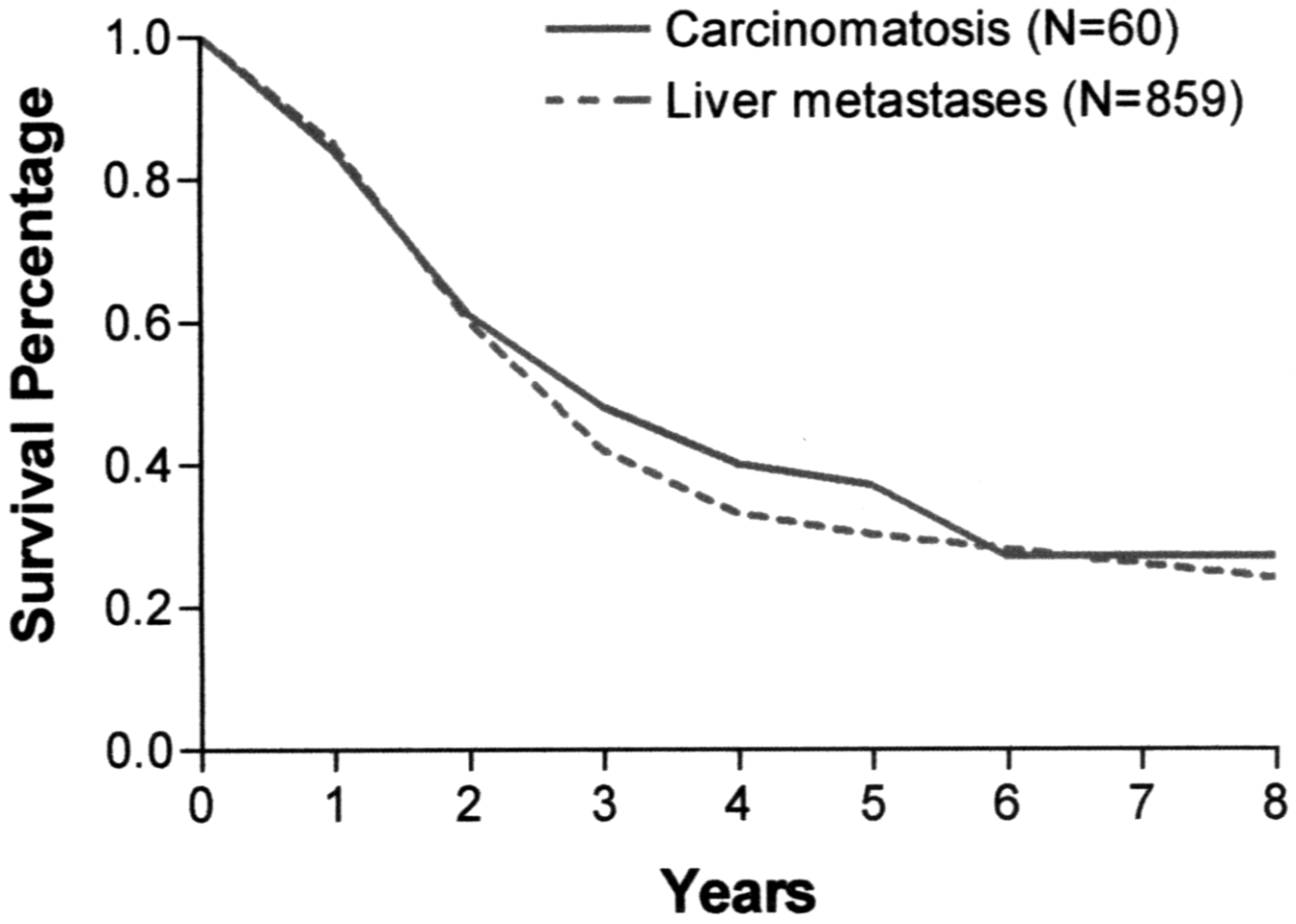
Phase II studies from 28 institutions 1995-2010.

Multiinstitutional French Study – Elias, JCO 2010 (N=523)

Multiinstitutional Dutch Study – Verwaal, Cancer Journal 2010 (N=562)

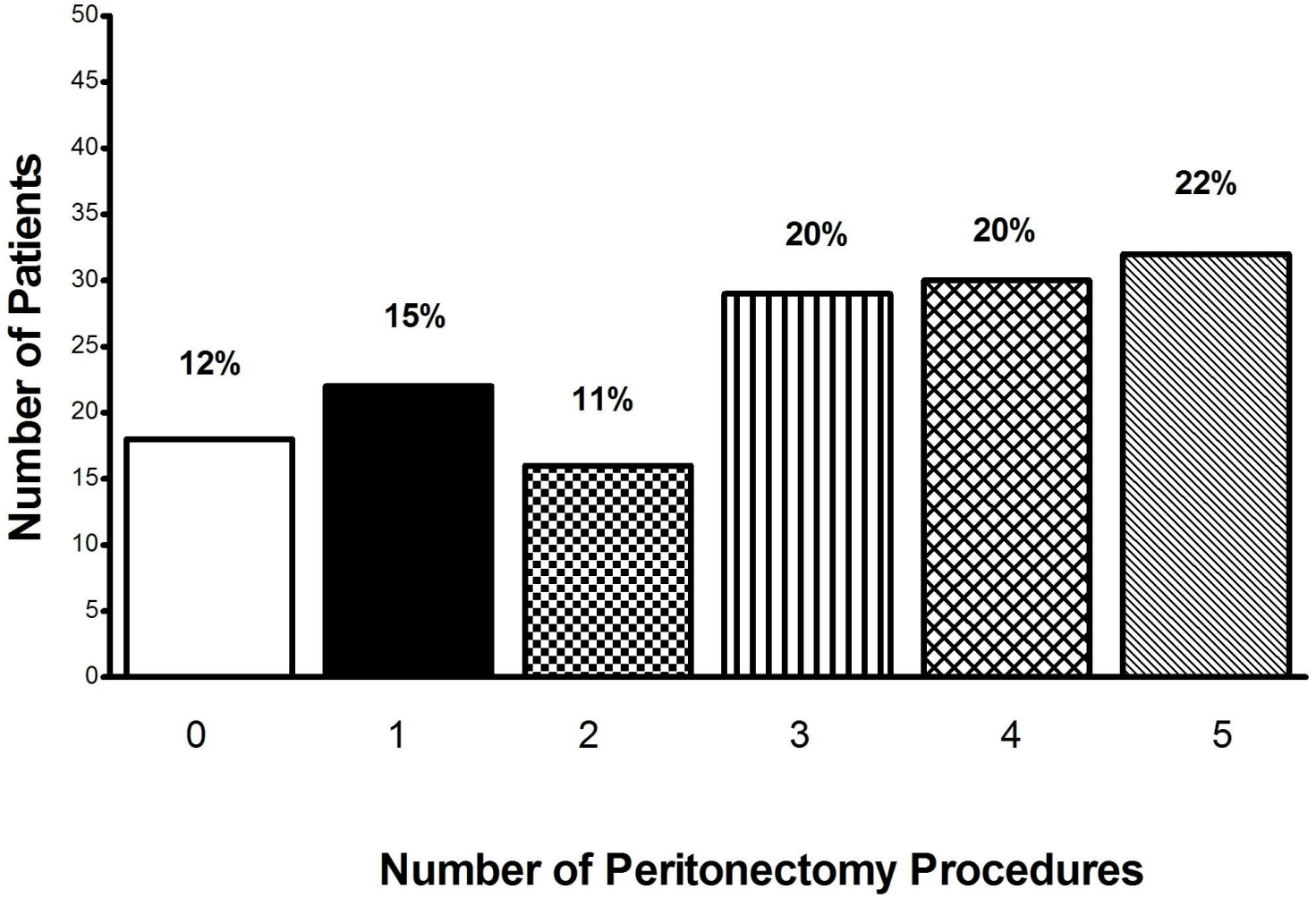
Median survival CC-0/CC-1 resection 35-60 months with 30-50% 5-year survival

Comparison of survival curves of a group of patients with colorectal metastases to the liver and a second group with peritoneal carcinomatosis.

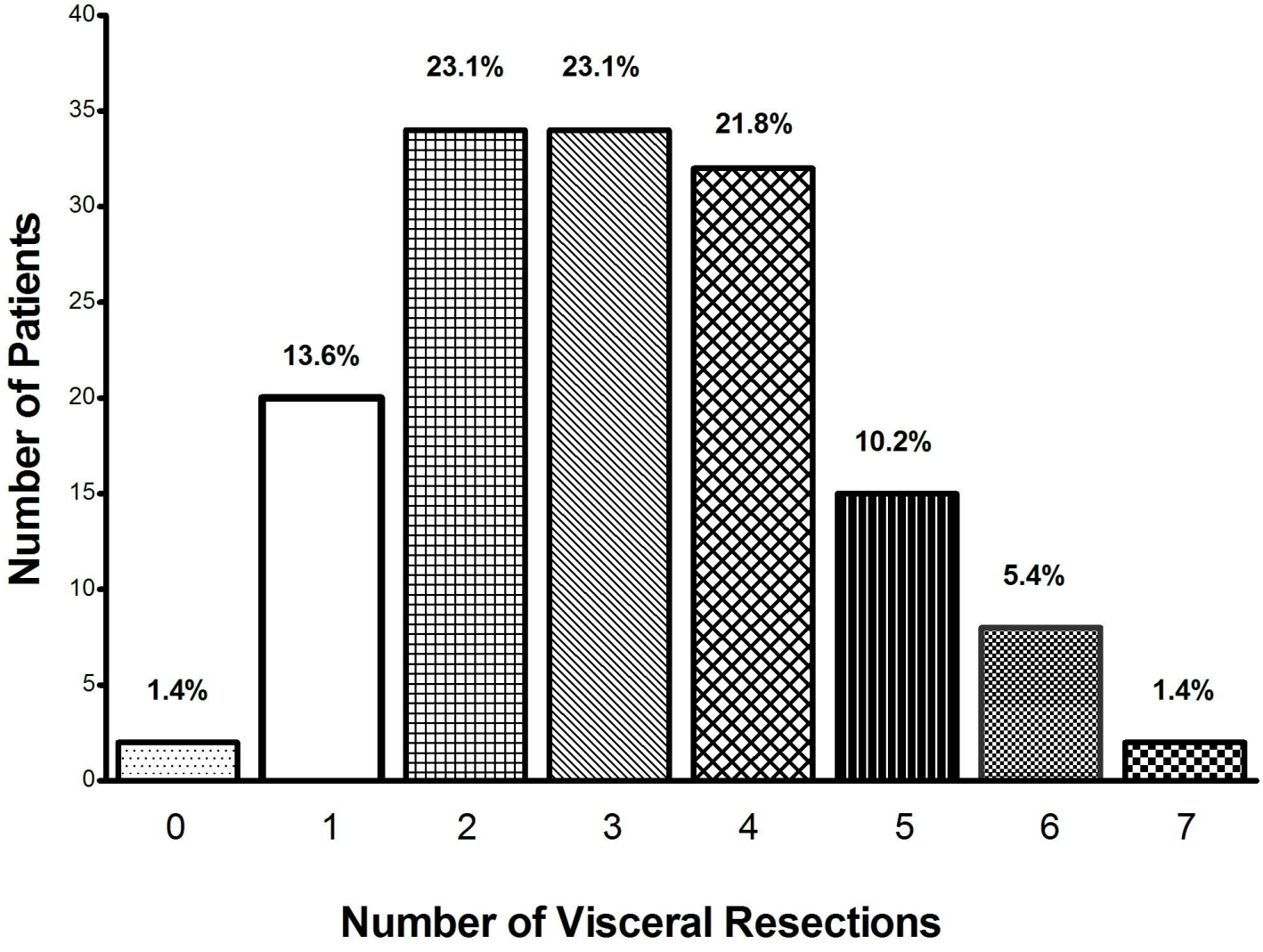


Gertsch P. Surg Oncol Clin N Am, 2003

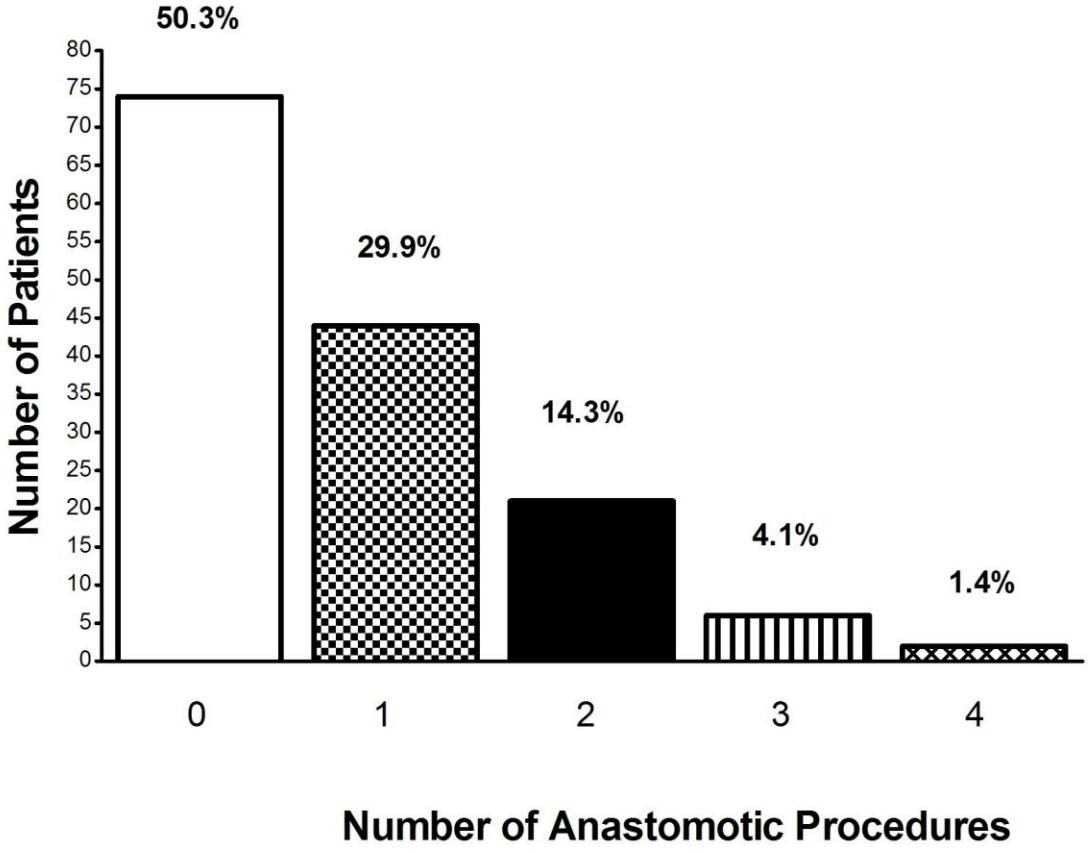
Morbidity and mortality of 147 consecutive colorectal and appendiceal carcinomatosis patients treated with CRS and HIPEC – 5-FU



60% of patients had 3 or more peritonectomy procedures

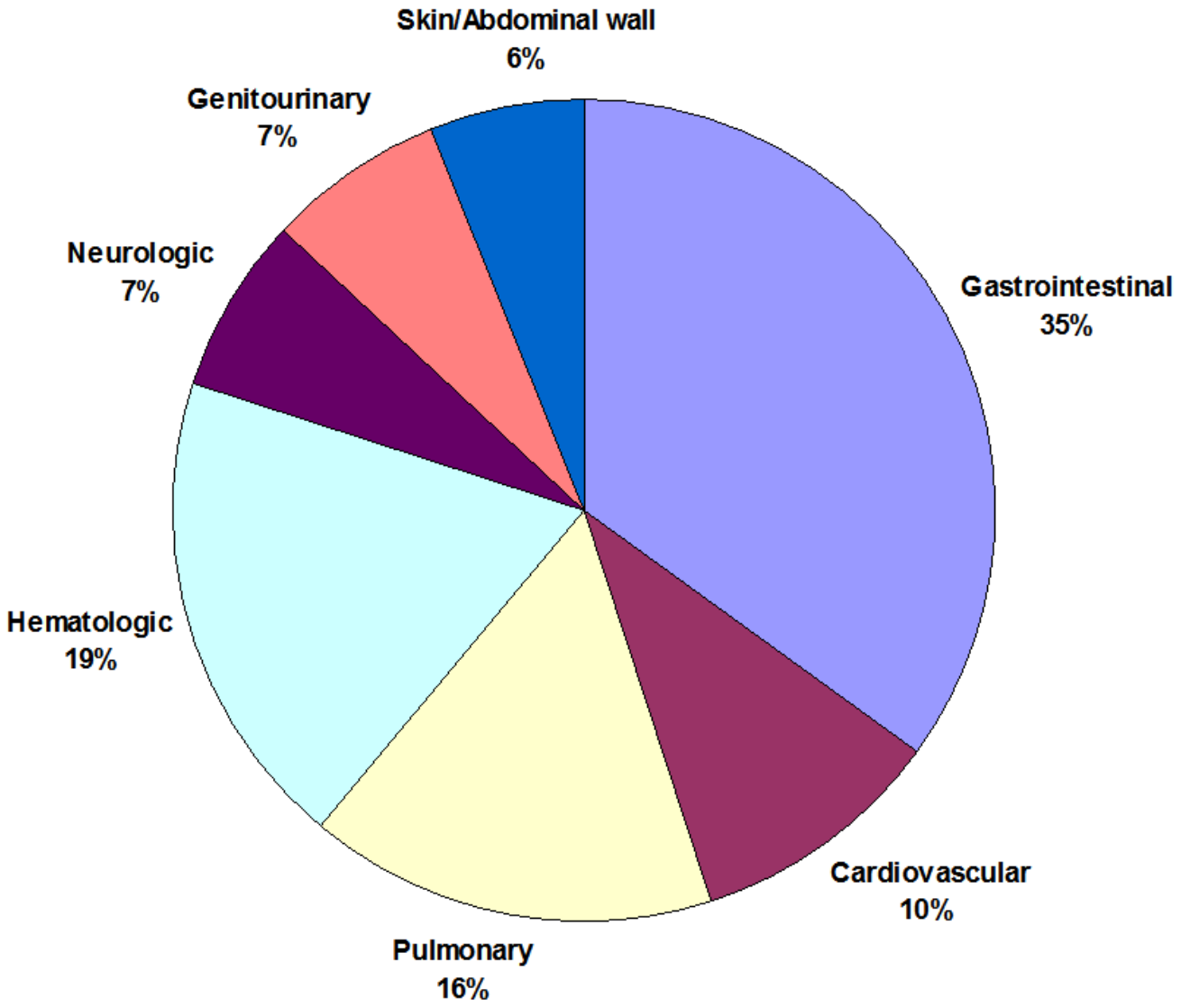


85% of patients had 2 or more visceral resections



50% of patients had at least 1 anastomosis

Grade IV adverse events occurred in 18 (12%) of the 147 patients treated. There were a total of 31 grade IV adverse events and a single mortality.



CRS and HIPEC for Colorectal Carcinomatosis

Credits

- Long-term survival in 20-50% of patients
- Selection factors have been well defined
- An important addition to the MDT for management of colorectal malignancy
- Morbidity (12%) and mortality (1%) at experienced centers is acceptable

Debits

- Many patients treated for a few to benefit
- The surgical technology is complex and requires an extended learning curve
- Referral by medical oncologist are often late with a large extent of disease
- So far a uniform HIPEC treatment has not emerged; perioperative chemotherapy needs to be optimized