

Update on Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Peritoneal Carcinomatosis

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Learning Objectives

- 1. To compare potential treatment options for colorectal and appendix carcinomatosis
- 2. To be aware of data supporting cytoreductive surgery and heated intraperitoneal chemotherapy in the treatment of colorectal and appendix carcinomatosis

Learning Questions

- 1. Standard of care for the treatment of low grade appendix carcinomatosis is:
 - a) Palliative care
 - b) Palliative chemotherapy
 - c) Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC)
 - d) Debulking surgery

Learning Questions

- 2. Standard of care for the treatment of colorectal carcinomatosis is:
 - a) Palliative care
 - b) Palliative chemotherapy
 - c) Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC)
 - d) Debulking surgery

Learning Questions

- 3. Level one evidence supports the use of cytoreductive surgery and HIPEC in selected patients with colorectal carcinomatosis

- True or false?

Case Presentation

- 29 y.o. female presents with 24 hr history compatible with acute appendicitis vs. pelvic inflammatory disease
- Similar discomfort and vague bloating x 4 months
- Now what?

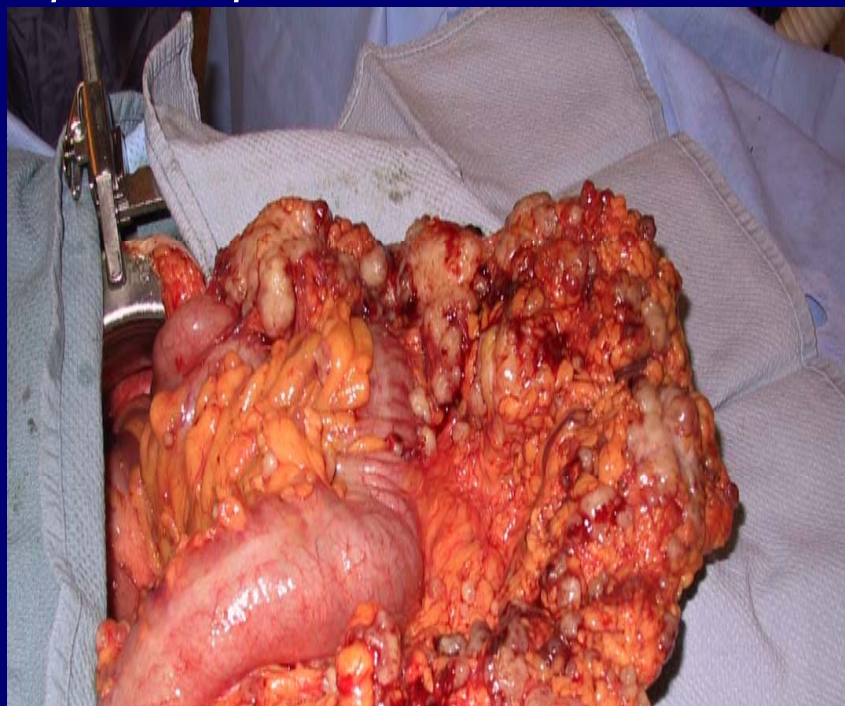




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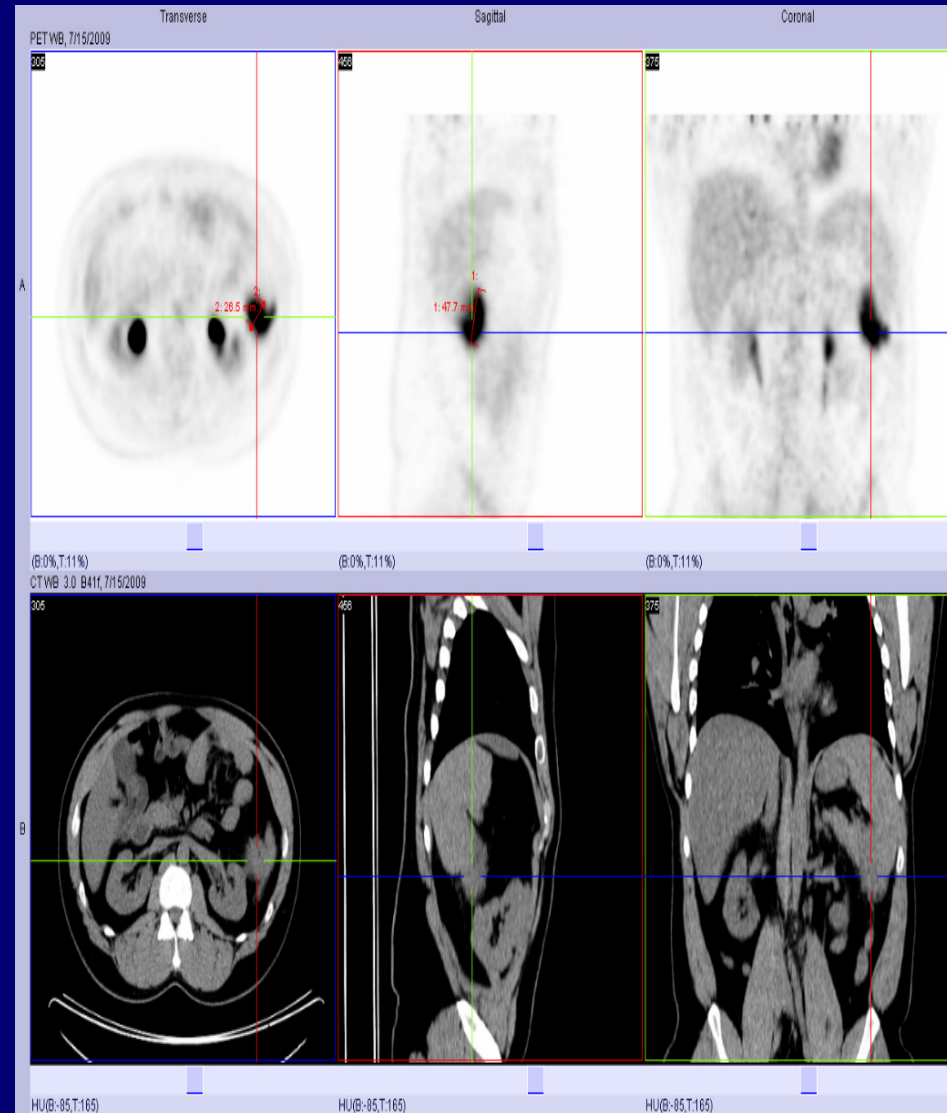
Case Presentation

- 58 y.o. female with Rt colon cancer
- Pre-op CT/Ix negative
- At time of laparotomy, evidence of peritoneal nodules in omentum, RLQ, and cul de sac
- Options?
 - 1) open/close
 - 2) remove right colon
 - 3) debulk?
 - 4) palliative chemotherapy



Case Presentation

- 53 y.o. female with prior extended right hemicolectomy 2 yr previous for T3N1 tumor
- Adjuvant FolFox
- Now rising CEA with PET/CT suggesting peritoneal disease Lt pericolic gutter, cul de sac
- Options?

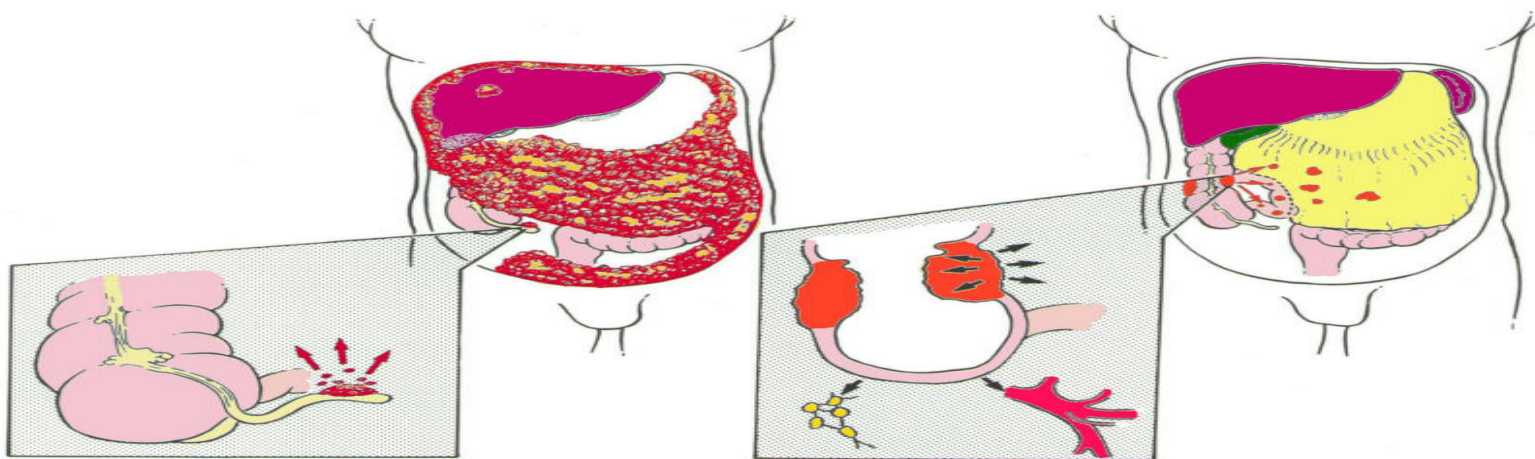




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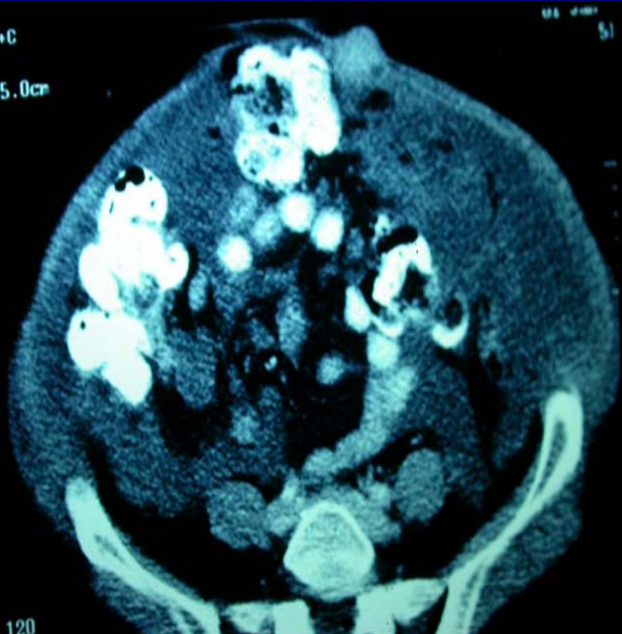
Introduction

- Definitions, primary tumors treated with cytoreductive surgery and heated intraperitoneal chemotherapy (CS/ HIPEC), indications, contra-indications
- **University of Calgary Experience**



Pseudomyxoma Peritonei

- Rare (?) clinical syndrome – “untrue mucinous tumor of the peritoneum”
- First described in 1884 – reaction of peritoneum to jelly like material produced by ovarian neoplasm
- First associated with appendiceal mucocele in 1901



Spectrum of Disease

- **Definition** – clinicopathological entity
- Mucinous ascites, mucinous implants in a typical distribution associated with a mucinous tumor of the appendix
- **DPAM** – disseminated peritoneal adenomucinosis (from cystadenoma)
- **PMCA** – peritoneal mucinous carcinomatosis (from cystadenocarcinoma)
- **PMCA** – intermediate category

Adenomucinous?

- DPAM- disseminated adenomucinosis implies benign disease
- Life-threatening, uniformly fatal disease without treatment
- Newer classification

low grade adenocarcinoma

high grade adenocarcinoma

Rare?

- National pathologic database study – Netherlands
- 167,744 appendectomies – (1995-2005)
- 1482 appendiceal lesions (0.9%)
- Nine percent of these developed PMP
- Mucinous epithelial neoplasms identified in 0.3% - of these, 20% developed PMP
- Incidence approx. 2/ million/ year
- 10% had colonic lesions

Prior Standard Treatment

- Serial Debulking
- 97 patients – 1980-2002 – highly selected
- 2.2 operations (range 1-6)
- 55% complete cytoreduction
- 91% disease recurrence; median dfs 24 months
- 10 year survival in 21% (majority with low grade biology)

Colorectal Carcinomatosis: Standard Treatment

- **Poor prognostic sign** - dismal quality of life
- Involves ~25-30% of all CRC pts; 5-8% at time of primary surgery; ~25% of pts with recurrent disease
- **Palliative Therapies**– 4-6 month median survival – survival beyond 2 yrs rare; uniformly fatal
- New chemotherapeutics in Stage IV colorectal cancer – med 19- 22 month survival – carcinomatosis population not specifically studied

Cytoreductive Surgery (vs. Debulking)/HIPEC Combined Modality Treatment

- **Complete removal of all macroscopic tumour**

- Greater omentectomy-splenectomy
- LUQ peritonectomy/ RUQ peritonectomy
- Lesser omentectomy-cholecystectomy
- Pelvic peritonectomy
- Abdominal organs involved with tumour

**Directed
resection**

- **Lysis of intra-abdominal adhesions**
- **Exposure to heated chemotherapy**
- **Reconstitute GI tract (usually after chemotherapy)**



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Peritoneal Cancer Index (PCI)

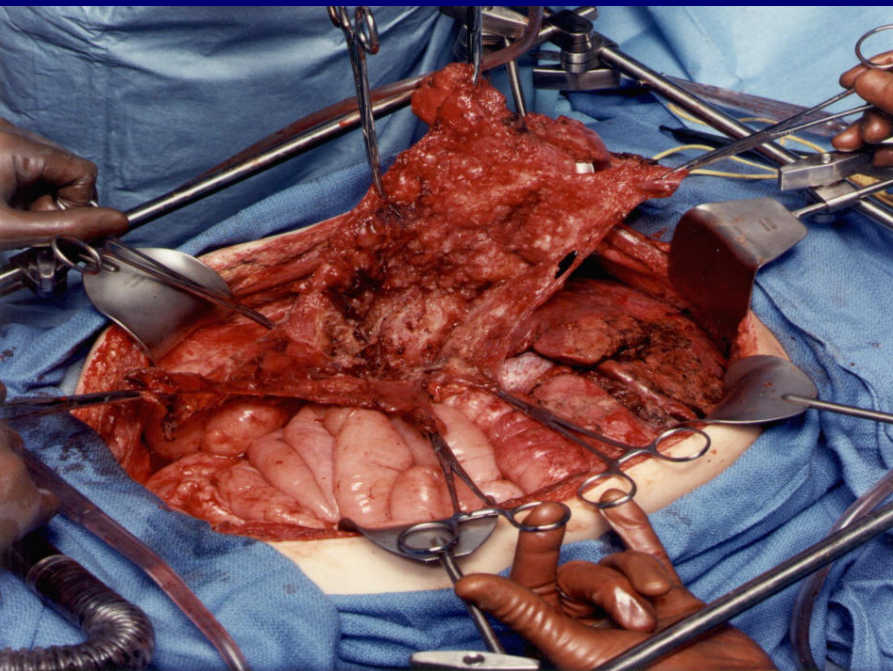
Lesion Size Score

LS 0 – no tumor seen

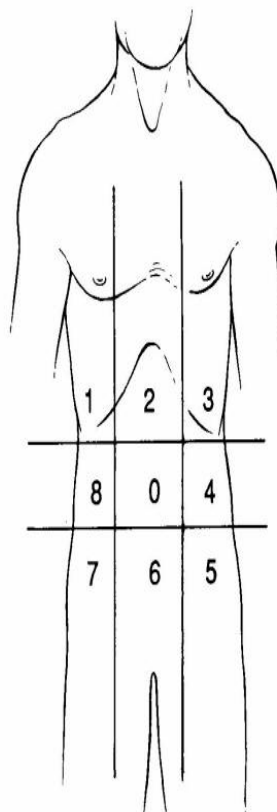
LS 1 <5mm

LS 2 – 5 mm-5cm

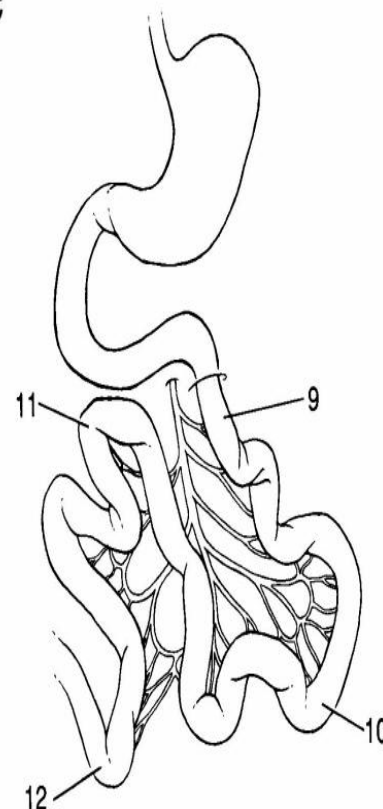
LS 3 > 5cm/ confluent



ABDOMINOPELVIC REGIONS 0-12



- 0: Central
- 1: Right upper
- 2: Epigastrium
- 3: Left upper
- 4: Left flank
- 5: Left lower
- 6: Pelvis
- 7: Right lower
- 8: Righth flank



- 9: Upper jejunum
- 10: Lower jejunum
- 11: Upper ileum
- 12: Lower ileum

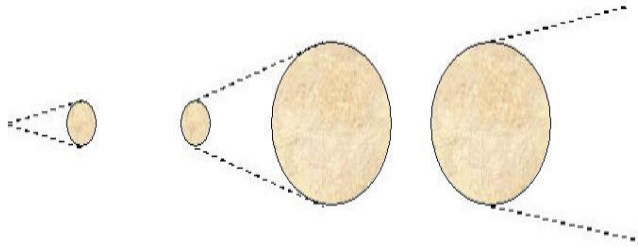
Completeness of Cytoreduction Score

CC-0

CC-1

CC-2

CC-3

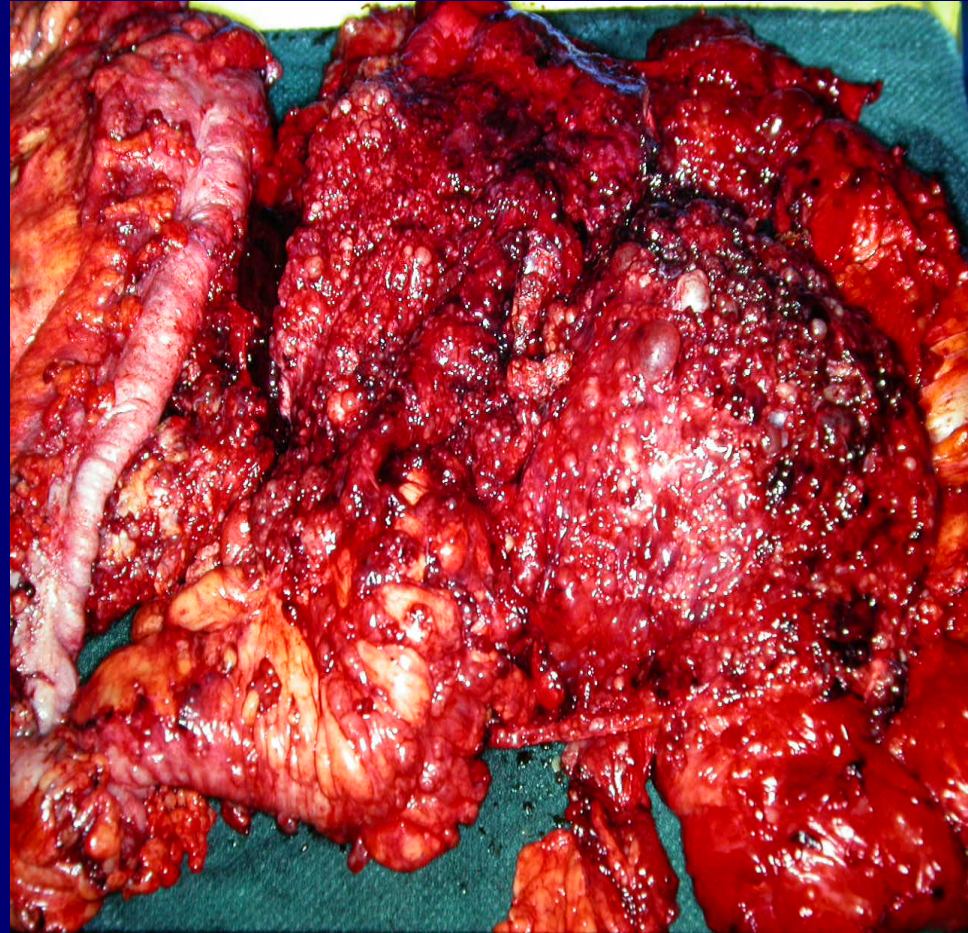


No Disease

Present <0.25 cm

0.25 cm - 2.5 cm

> 2.5 cm





Hyperthermic Chemotherapy

- Direct **cytotoxic** effect – impairs DNA repair, denaturation of proteins, induction of heat-shock proteins, induction of apoptosis, inhibits angiogenesis, inhibits oxidative metabolism
- Temperature – dependent
- Time/ Exposure – dependent
- **Synergism** with cytotoxic drugs

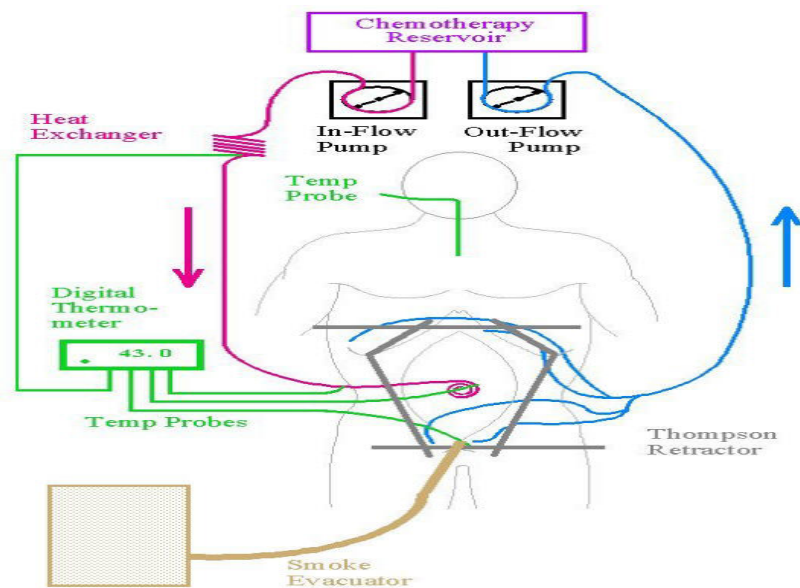
Synergism		Cell-cycle NS
Mitomycin C	Yes → 39°C	Yes
Cisplatinum	Yes → 39°C	Yes
Melphalan	Yes → 39°C	Yes
Mitroxantrone	Yes → 39°C	Yes
Oxaliplatin	Yes → 39°C	Yes
Doxorubicin	Yes – threshold 42°C	Yes
Irinotecan	No	Yes
5 FU	No	No



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Heated Intraperitoneal Chemotherapy

- Pharmaceutical advantages:
- Surgery separates adhesions and debulks tumor
- Peritoneal concentration $>$ plasma; high mol wts
- Synergy with heat



Ongoing Study of Regional Treatment For Peritoneal Carcinomatosis

- **February 2000 to January 2008 (Protocol 1)**
- 101 consecutive patients with peritoneal carcinomatosis explored with intent of CS/ HIPEC using standard protocol
 - CS + HIPEC (MMC) and early postop intraperitoneal chemotherapy (EIPC) 5FU X 5 days
- **February 2008-June 2009 (Protocol 2)**
- 65 consecutive patients with new protocol (now≈164)
 - CS + HIPEC (oxaliplatin) + IV 5FU

Am J Surg 2009;197:614-8

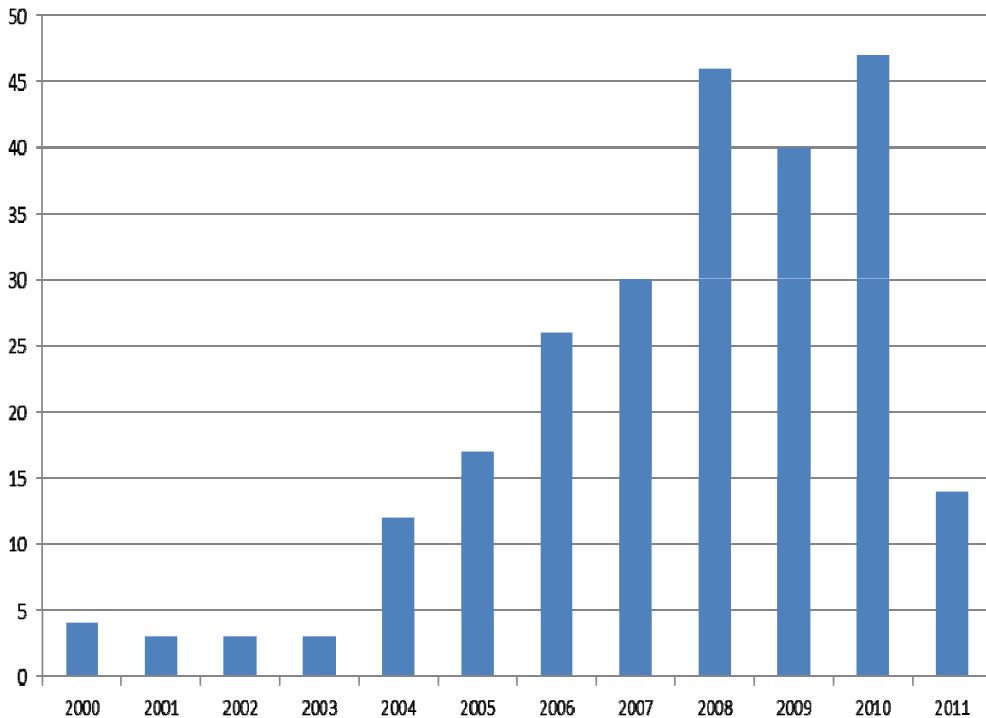
Ann Surg Oncol 2010;17:Suppl; Am J Surg 2011;201:645-9



Accrual Pattern / Pathologic Diagnoses

Number of patients undergoing cytoreduction surgery

265



Appendix	159
Colon/Rectum	79
Mesothelioma	10
Primary Peritoneum	7
Small Bowel	5
Ovary	2
Stomach	3

Results

- 166 patients explored
- 139 (84%) had complete macroscopic tumor excision (CC-0)
- 27 (16%) had persistent macroscopic residual disease
 - 8 minimal (CC1) and 19 significant (CC2+)
- 142 (85%) patients received HIPEC, 84 patients received HIPEC + EIPIC (early protocol)

Patient Characteristics

Age (Median/Range)	52 / 18-79
Sex (Female/Male)	90 / 76
LOS (Mean/Range)	23 / 5-59
PCI Score (Mean/Range/ Mode)	21/0-39/39



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Perioperative Data

Residual Disease (CC 0/1/2-3)	139 / 8 / 19
Operative Time in Minutes (Mean/Range)	380 / 63-690
Estimated Blood Loss in mL (Mean/Range)	1190 / 0-4800
Red Blood Cells in Units (Mean/Range)	1 / 0-17
ICU Admission Post-op (%)	35

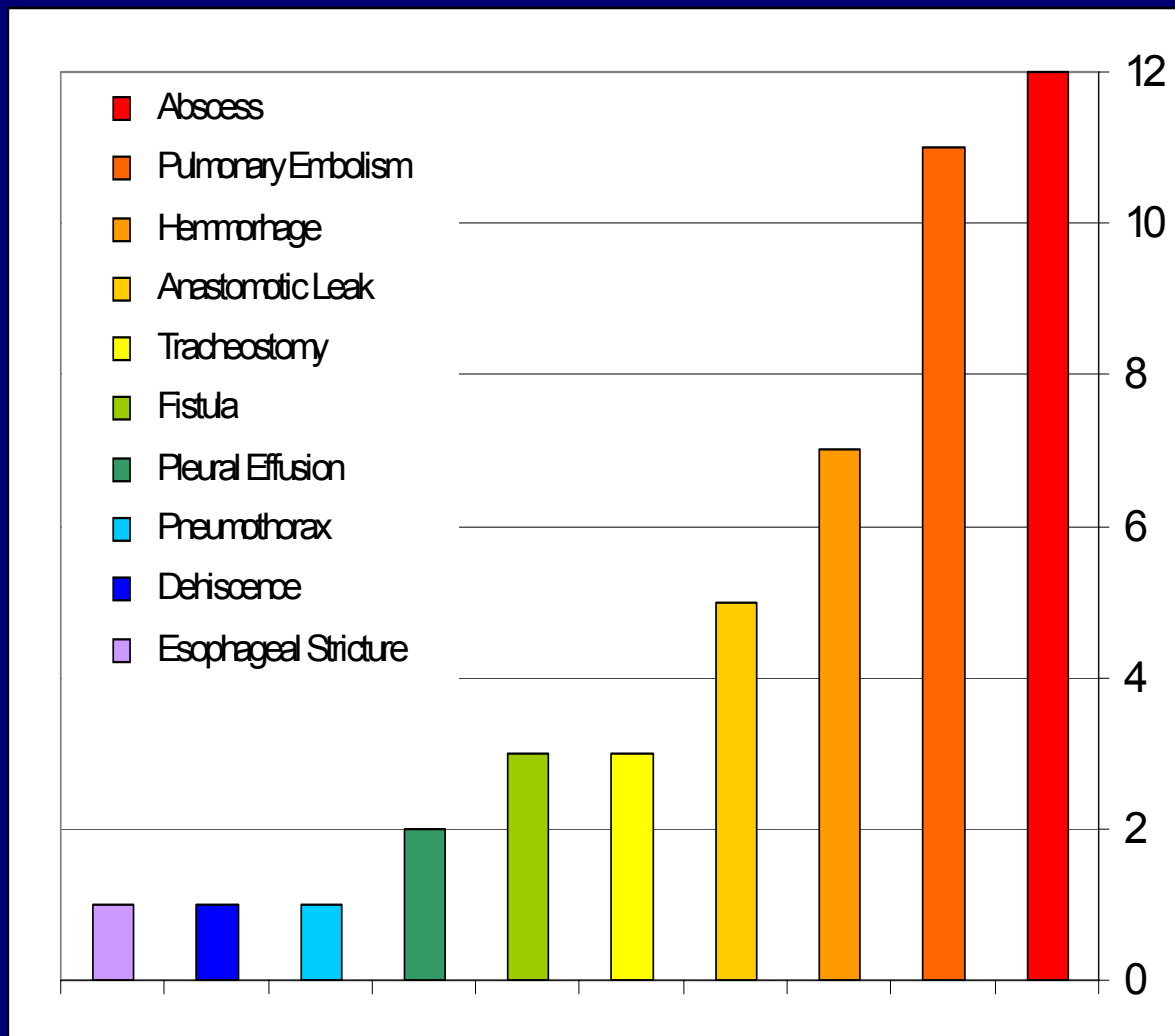
Peritoneal Cancer Index

- A significant proportion (71%) were found to have a Peritoneal Carcinomatosis Index (PCI) > 13 indicating large burden disease
- Median PCI = 21 (49% had PCI > 20)
- Appendix Median PCI = 23 (51% had PCI > 20)
- Colorectal Median PCI = 14 (35% had PCI > 20)



Complications

- 4 treatment related deaths (MR 2.4%)
- 34% patients experienced a major complication (grade III, IV, or V)
- 10% patients required a subsequent operation
- 5 patients required early termination of EIPIC due to complications



First Protocol (HIPEC + EPIC) vs. Second Protocol (HIPEC + IV5FU)

Outcome	Group 1 (101)	Group 2 (65)	p	Literature
LOS (days)	21.5	16	0.033	11-29 ¹
Complication	39.3%	25.6%	0.181	12-68% ²
Mortality	3.9%	0.0	0.790	0-9% ²
EBL (cc)	1200	600	<0.001	650-940 ³
Operative Time (min)	405	360	0.508	450-500 ³
ICU admission	45.2%	23.3%	0.026	unavail.

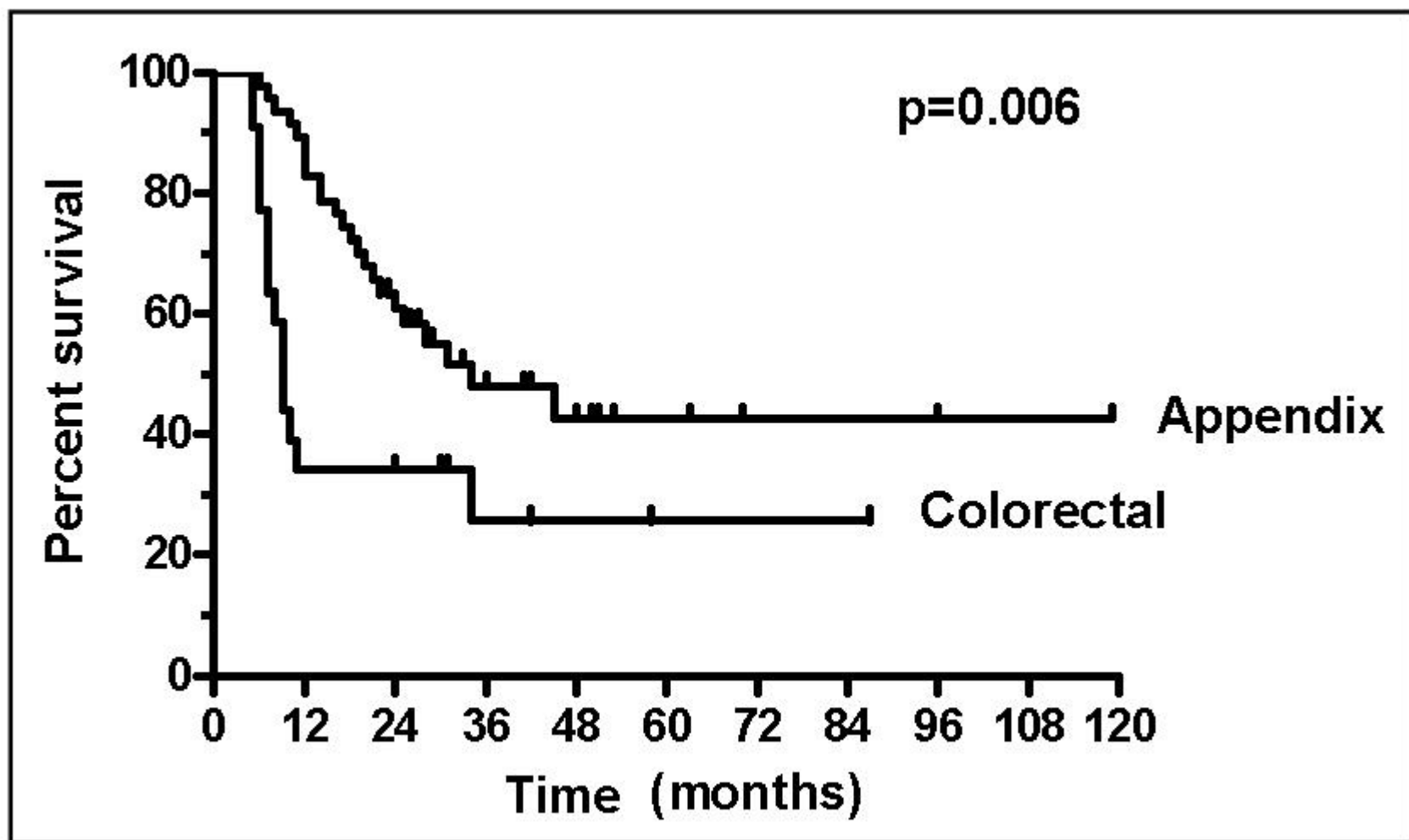
- How can we account for improvement over time?
- Chemotherapy/ protocol change, increased proficiency with procedure, other practical changes – antibiotic change, LMWH, minimize drains, ICU/chest tubes for diaphragm stripping

Survival

- First protocol – 2000-2008
- Median follow-up 29 months (range 1-119)
- One patient lost to follow-up at 3 months
- No evidence disease (NED) - 37%
- Alive with disease (AWD) - 20%
- Died with disease (DWD) - 43%



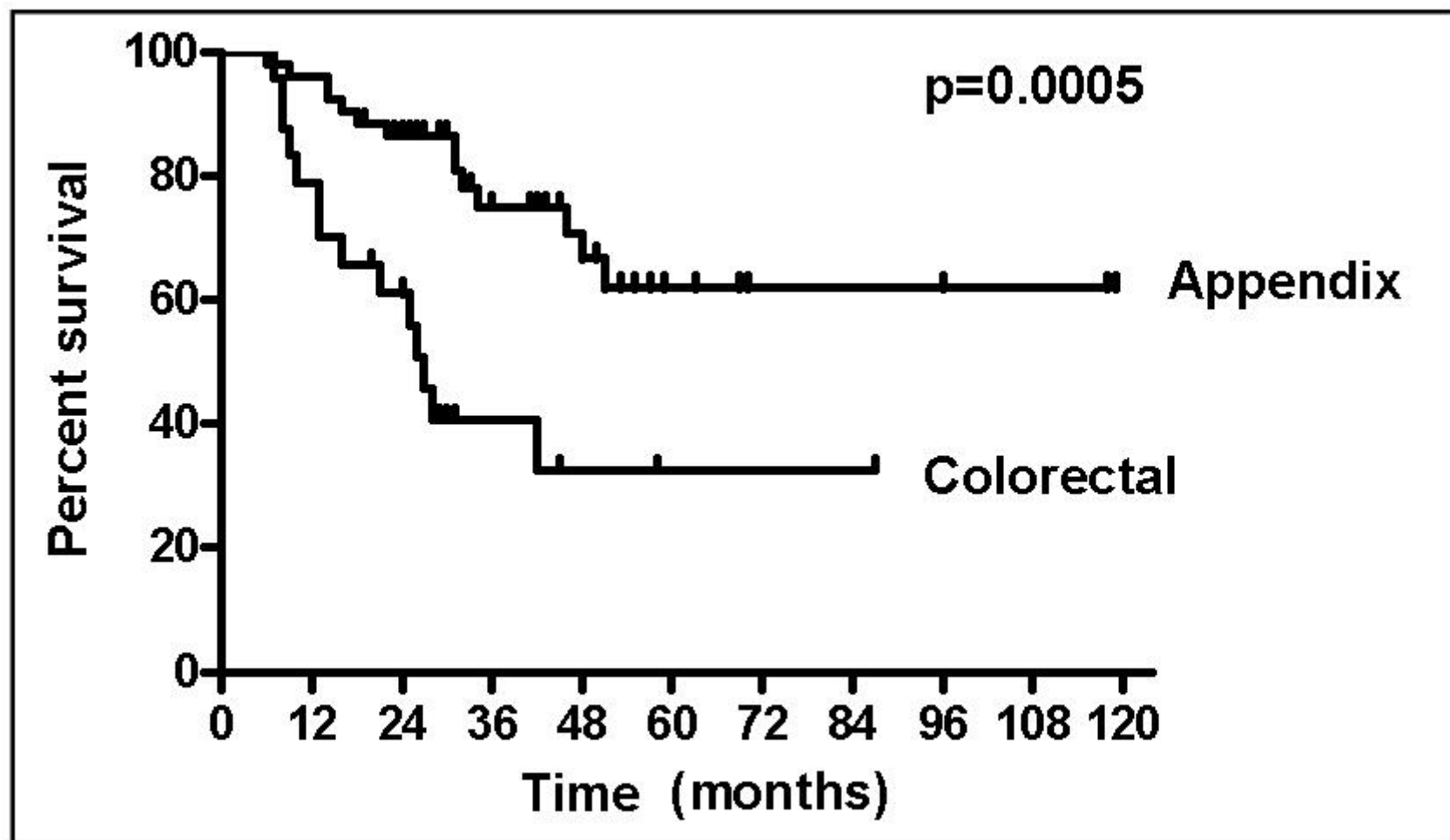
Disease-Free Survival





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Overall Survival



Summary - Appendix

- Disease free survival (DFS) – median 34 months
- Overall survival (OS) - has not yet been reached

3-year

5-year

DFS 48%

OS 76%

DFS 42%

OS 62%

Summary - Colorectal

- Disease free survival (DFS) – median 9 months
- Overall survival (OS) – median 27 months

3-year

5-year

DFS 34%

DFS 26%

OS 38%

OS 34%

Comparison of Long-term Results

Table 1 Comparison of long-term results: appendix

	n	MFU, mo	3-y DFS, %	3-y OS, %	5-y DFS, %	5-y OS, %	Disease status, %		
							NED	AWD	DWD
Current Study	58	32	48	76	42	62	45	21	34
Zoetmulder ⁶	103	52	44	71	37	60	61	20	19
Sugarbaker ¹⁹	501	48	-	-	-	-	47	15	32

MFU - median follow-up, NED - no evidence of disease, AWD - alive with disease, DWD - died with disease

Table 2 Comparison of long-term results: colon

	n	MFU, mo	3-y DFS, %	3-y OS, %	5-y DFS, %	5-y OS, %
Current Study	31	25	34	38	26	34
Zoetmulder ²⁰	117	22	-	28	-	19
Glehen et al. ¹⁵	506	53	16	39	10	19
Elias et al. ¹⁶	523	45	-	-	10	27

MFU - median follow-up

Protocol Summary

- Long-term results from the current protocol demonstrate improved DFS and OS for the treatment of PC
- Similar to results published at other major centers
- Severity of disease by PCI alone is not a patient selection criterion at our center (have not found PCI to be predictor of CC-0 resection)

Protocol Conclusions

- Significant difference in appendiceal and colorectal survival
- Prior to advent of CS and HIPEC, 35% 5-year OS not achieved in colorectal PC
- Importance of pre-op patient selection
 - Routine PET?
 - Trial of pre-op systemic chemotherapy?
- Importance of post-operative treatment
 - Most patients received postop 'adjuvant' systemic chemotherapy
 - Colorectal carcinomatosis; high grade appendix tumors

Candidate for CS/ HIPEC?

- **Contra-indications**

- Poor ECOG status, medically unfit
- Extra-peritoneal disease
- Evidence of biliary, urinary, bowel obstruction
- Gross disease in small bowel/ mesentery
- Massive periportal disease/ retroperitoneal disease

- **Pre-Treatment Investigations**

- CT for anatomic imaging; CT/PET to r/o distant disease in tumors other than pseudomyxoma

- **Pre-Treatment Considerations**

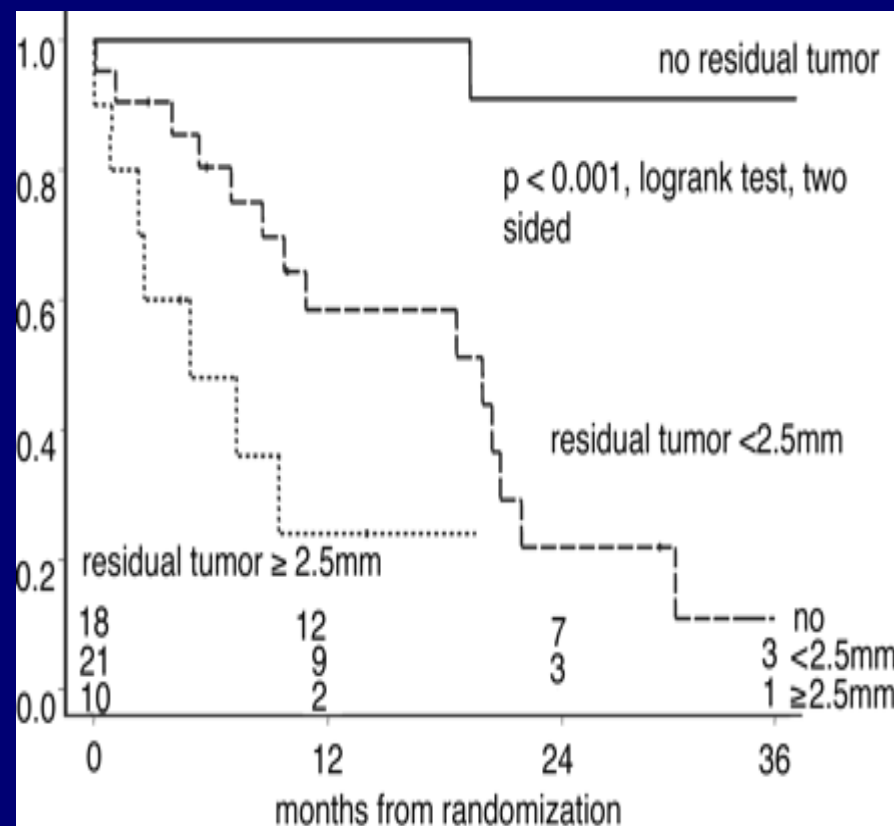
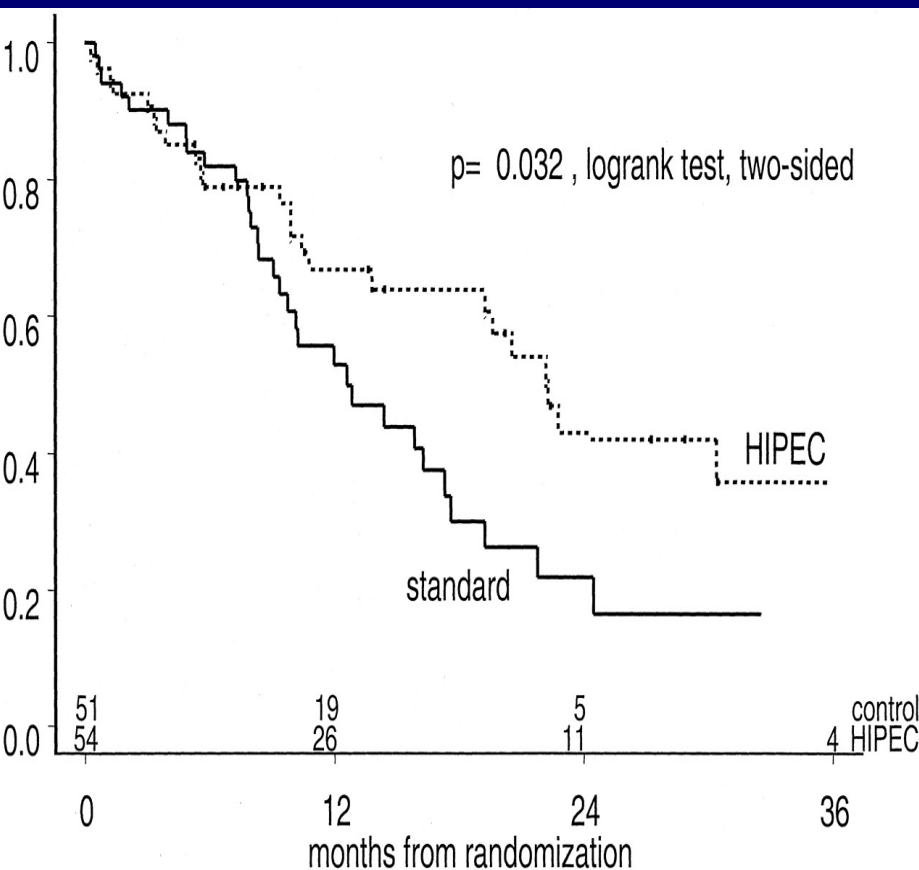
- Trial of systemic chemotherapy if significant disease (Standard of care)
- If found at surgery, partial debulking generally not helpful

Randomized Control Trial

- 105 pts randomized to palliative intent chemotherapy vs. cytoreduction + HIPEC (MMC)+ adjuvant chemotherapy
- Well balanced groups although 11 and 7 appendix pts in chemotherapy grp and HIPEC group respectively
- Experimental arm – 18 CC0, 21 CC1, 10 CC2
 - 4 deaths (8% MR); 15% GI fistula, 8% hemorrhage, 15% leukopenia
- Intent to treat analysis

Survival Analysis

22.3 m vs. 12.6 m



Long-term Data

- 117 patients – 1995-2003 – overlap with RCT
- Median overall survival 21.8 months
- 1,3, and 5 yr os – 75%, 28%, 19% respectively
- 59 patients – complete cytoreduction
- Median overall survival 42.9 months

Multi-Center Trial

- **Colon Cancer Treatment – 506 patients**
- Morbidity – 23%; Mortality – 4%
- Median Survival 19 months
 - If Complete Treatment (55%) – 32 months
 - If Incomplete Treatment – 8 months
- Overall – 1 yr 72%, 3 yr 39%, 5 yr 19%
- Disease-free – 40%, 16%, 10% respectively

Systematic Review

- **Medline search 1950-Feb 2009**
 - 4 comparative studies, 43 observational studies
- **Cytoreduction + HIPEC** – significantly improved survival compared to palliative approach
- **Study sample** – 15-523 pts; F/u 10-86m
- **1 year** – 55-100%; **3 year** – 4-71%;
5 year – 11-28%



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Conclusions

- Growing body of literature, including Canadian, support the use of cytoreductive surgery and hyperthermic chemotherapy for appendiceal and colorectal carcinomatosis in properly selected patients
- Further studies, especially multi-centre prospective trials, required

Overall Future Directions

- 'Advanced GI Surgery' Clinic now established
- Establishment of a National Group – Halifax, Montreal, Calgary, Edmonton, Toronto
- CHiCG (Canadian Hipec Collaborative Group)
- Development of synoptic operative reports
- ?future Canadian trials

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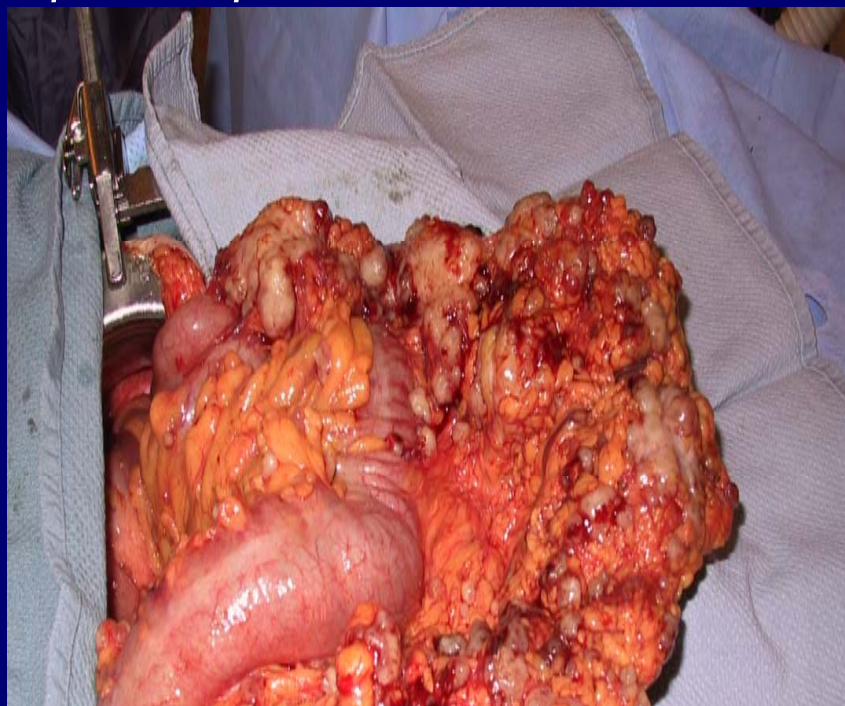




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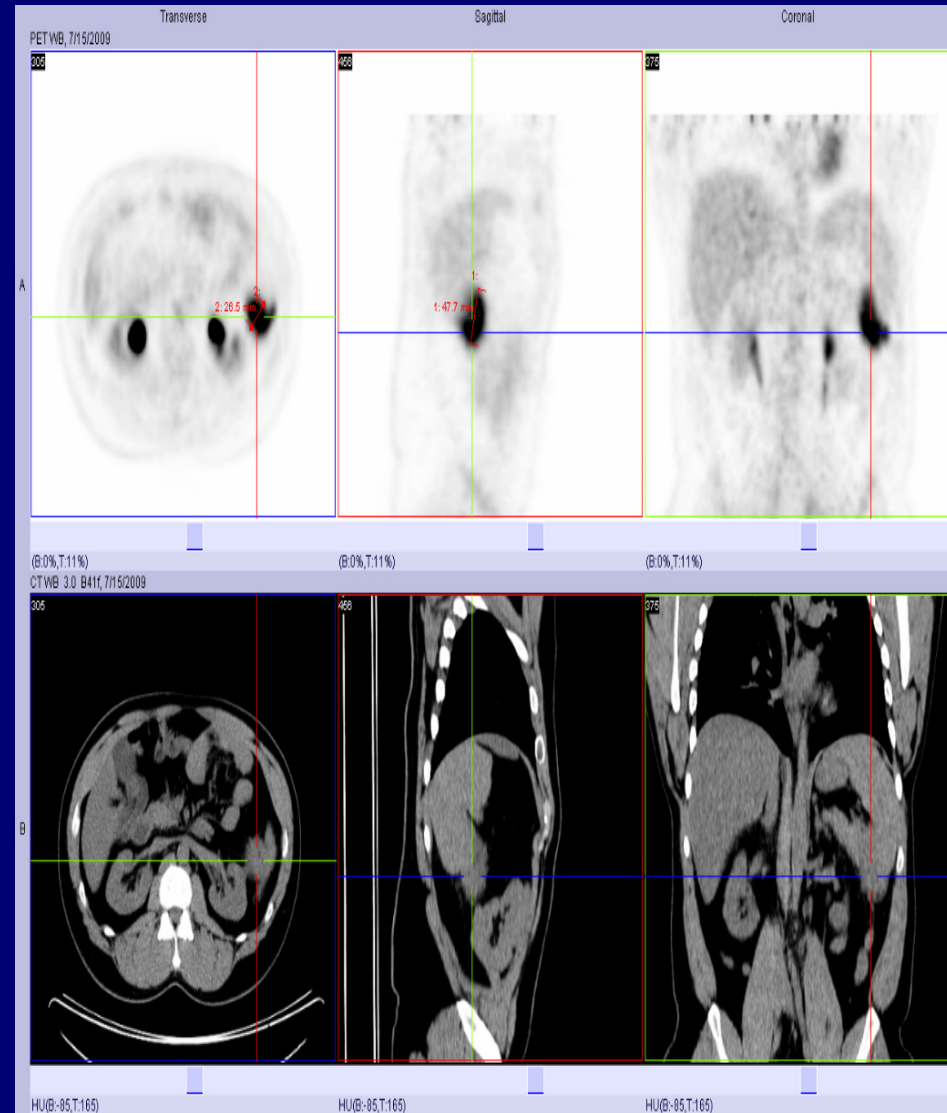
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Questions?

- **Acknowledgements:**

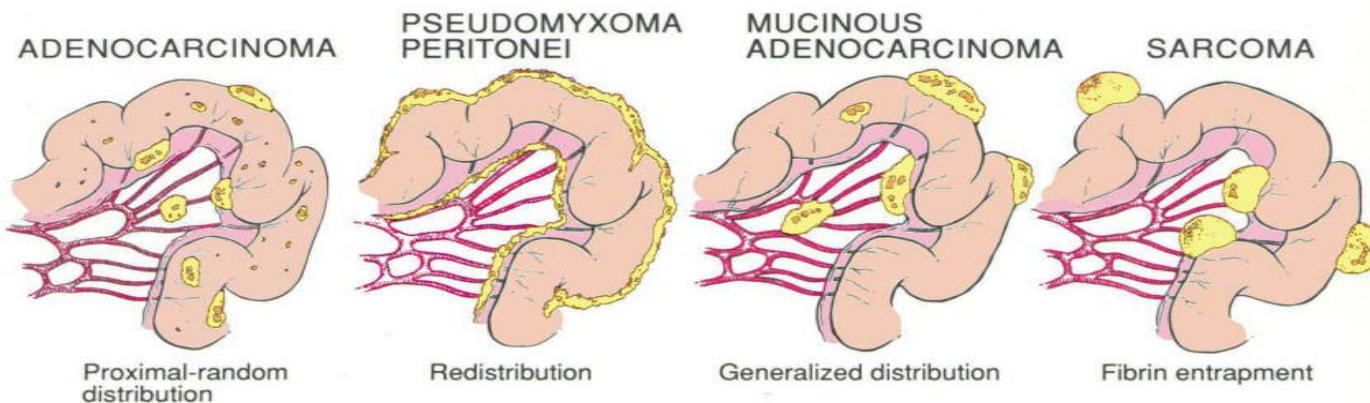
Dr. Walley Temple

Drs. Lanuke, Francis, Hamilton, McConnell

'Team' – surgical colleagues, medical oncology colleagues, surgical team, perfusion team, anesthesia colleagues, intensivists, Unit 102, administrative assistants, administration,

Other Tumor Subtypes

- Similar rationale; More difficult tumor biology and less data
- Considered: Mesothelioma, Stomach, Ovary/ Primary Peritoneal, Small bowel, Sarcomatosis



Peritoneal Mesothelioma

- 10-20% of all malignant mesotheliomas
- Same rationale, pre-operative Ix
- Few (~10) published series – 12-62 pts
- Variable chemotherapeutics – MMC, Cisplatin, Cisplatin + doxorubicin
- Improved median (17-79; 26-30 most common) compared to palliative chemotherapy (9-15 m med)

Gastric Cancer

- **Sytematic review** of 11 randomized trials with 'adjuvant' IP chemotherapy for resectable gastric cancer
- 1161 cases – 2 European, 9 Asian trials; only 3 trials of high-quality
- **Pooled Odds Ratio 0.51** (0.40-0.65) favoring addition of IP chemotherapy
- 2 and 3 yr survival 42 & 38% IPC ct 28 & 20% surgery
- Limited data in established peritoneal disease
 - Feasible in ~50% explored, median survival 8-11 months, 5 yr survival 6-16%

Ovarian Cancer

- 3 Randomized trials and Cochrane Review support intraperitoneal chemotherapy in the treatment of ovarian cancer
- Median PFS 18 vs 23.8 months ($p=0.05$)
- Median OS 48.7 vs 65.6 months ($p=0.03$)
- HR = 0.80 (0.69-0.90)
- However, very different multimodal treatment with cytoreductive surgical intent debulking < 1cm and IP chemotherapy given in a delayed fashion
- Currently, few centres (~50 pts) treat with CS/ HIPEC