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Cytoreductive Surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for the Treatment of Peritoneal Carcinomatosis.

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Case Presentation

Xx yo male

- No PMH/PSH
- Screening Colonoscopy (8/11) → Mid Transverse Colon mass → Mod. Diff AdenoCA

Preop w/u

- CT A/P: 2.8 x 1.7 cm mass within the mid transverse colon with non-specific LN's in the transverse mesocolon. No evidence of mets.
- CEA: 1.3

Plan: Laparoscopic extended right hemicolectomy

Case Presentation

OR (9/11)

- Lap → open
- Multiple SB mesenteric and pelvic implants
- Frozen section: carcinomatosis
- Nearly obstructing transverse colon mass

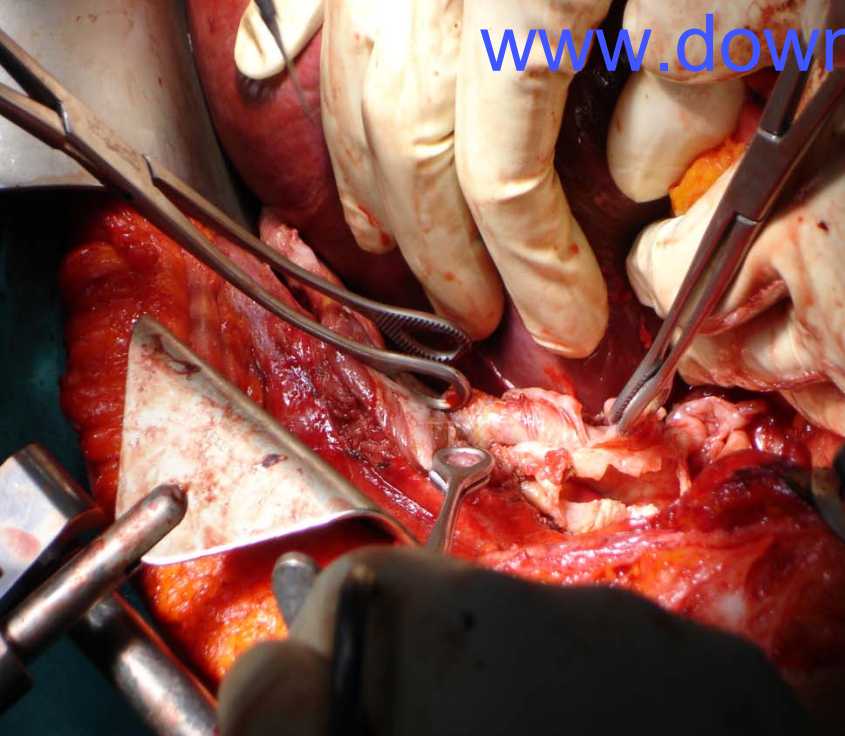
Procedure performed: Resection of mid-transverse colon mass with 1° anastomosis

- Postop course uncomplicated, d/c home POD#6
- Path: Mod diff. adeno CA Stage 4 (T₄N₁M₁)

Case Presentation

OR (10/11)

- Exlap, LOA
- Cytoreductive Surgery (CRS)
 - Partial peritonectomy, LAR, SBR w/ ileocecal resection, cholecystectomy, end colostomy
 - Peritoneal Cancer Index (PCI)= 12
- Hyperthermic Intraperitoneal Chemotherapy (HIPEC)
 - Mitomycin-C



Case Presentation

- Postop

SICU → POD#1 TPN

POD#10 → transferred to floor

POD#11 → adv. to clears

POD# 12

- severe RLQ pain, local peritonitis

- VS, blood work wnl

- CT A/P: Free air and extravasation in the RLQ

Case Presentation

OR

- Perforation near the intact staple line of the colonic side of the ileocolonic anastomosis
- Procedure: resection of the anastomosis, end ileostomy
- Path: Perforated ileocolonic anastomosis, no evid. of malignancy

Case Presentation

- Postop
 - SICU
 - IV antibiotics (WBC 19K)
 - Ostomy function POD# 3
 - TPN
 - POD#5 (WBC 9.5)
 - POD#8 advanced to clears, softs POD#10
- POD# 17 → Floor
- POD# 20 → 103°F →
 - SICU → TPN/central line d/c'd
 - WBC nml
- BCx/Ucx: Klebsiella → IV abx
- POD#29 → Floor
- POD#30 → d/c home
- Today: DOING WELL!!!**

- Carcinomatosis
 - Spread of tumor within the abdominal cavity
 - Initial surface involvements of the intraabdominal organs can later give rise to deeper invasion
 - Stage IV disease
 - Median Survival is 6-10 mths without treatment
- Cytoreductive Surgery (CRS)
- Hyperthermic Intraperitoneal Chemotherapy (HIPEC)





What Cancers Can Present with Carcinomatosis?

Aggressiveness

Gastric, Pancreatic, Small Bowel, Gallbladder

Colorectal

Ovarian

Appendiceal

Pseudomyxoma

Breast

Mesothelioma



Scope of the Problem

	# of patients
Gastric, Pancreatic, Small Bowel, Gallbladder	20,000
Colorectal	23,000
Ovarian	18,000
Appendiceal	1,200
Mesothelioma	<1,000

- About 25,000 patients are candidates for CRS + HIPEC
- 1,300 patients were treated with CRS + HIPEC in the US in 2009 (5.2%)

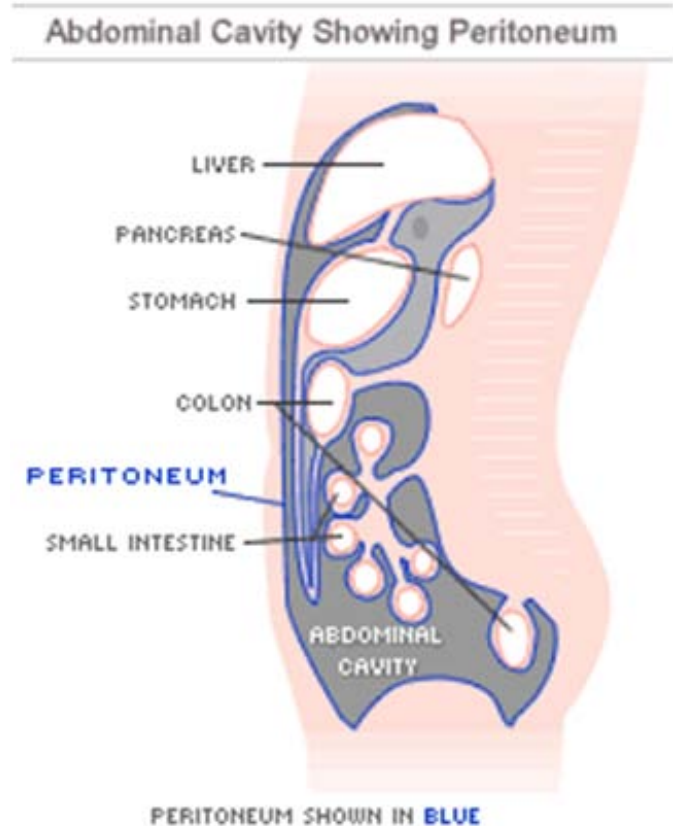
Treatment Options for Peritoneal Carcinomatosis

- Systemic Chemotherapy
- Abdominal port for chemotherapy dwell
- Radiation therapy
- Surgical therapy
 - Cytoreductive Surgery (CRS)
+ Hyperthermic
Intraperitoneal Chemotherapy
(HIPEC)



Rationale for CRS

- Peritoneum as a resectable organ
- Peritoneum as a locoregional site of extension, not distant, metastasis
- Goal: to resect all macroscopic disease



Rationale for HIPEC

- Intraperitoneal chemotherapy treatment immediately following tumor resection
- Ability to deliver:
 - higher dose chemotherapy within the peritoneal cavity
 - hyperthermia during treatment
- Hyperthermia
 - has direct lethal effects on tumor
 - potentiates the cytotoxicity of chemotherapy



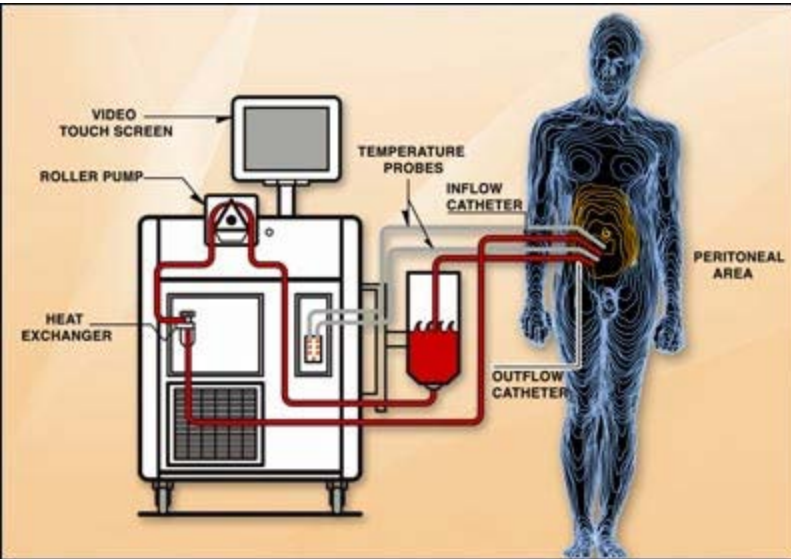
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Who is a candidate?

- Patients with abdominal carcinomatosis from GI, ovarian, primary peritoneal or mesothelioma origins
- No disease outside of the abdomen
- Good performance status (ECOG)

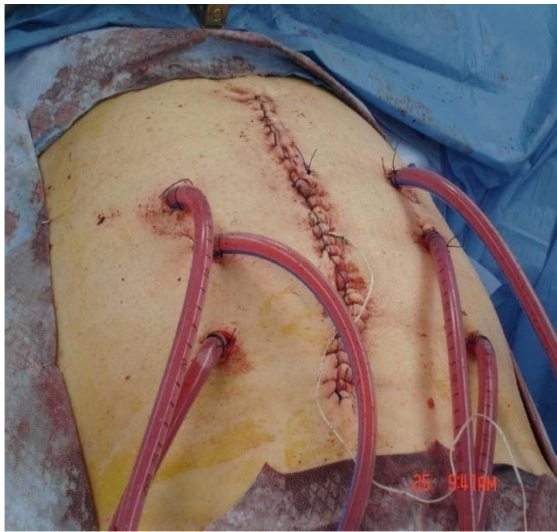
ECOG PERFORMANCE STATUS*

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

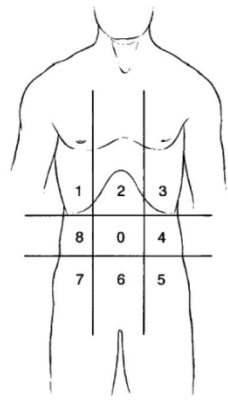
Operative Approach



- Exploratory Laparotomy, LOA, tumor debulking (CRS)
- Insertion of cannulas and temperature probes
- Close abdomen
- Connect perfusion circuit
- Circulate and heat
- Add drugs when temperature reaches 40°C (104°F)
- Perfuse for 60-120 mins while maintaining the temperature btwn $41-42^{\circ}\text{C}$
- Open abdomen and irrigate



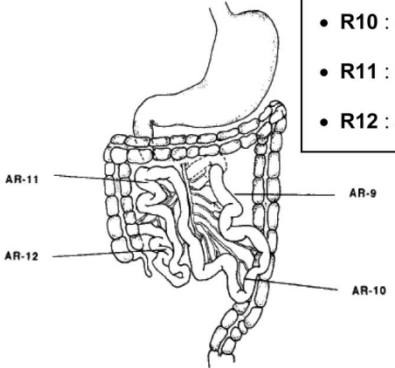
Peritoneal Cancer Index (PCI) de Sugarbaker



- Cotation by région :**
- 0 : no lesion
 - 1 : L ≤ 0.5 cm
 - 2 : 0.5 < L ≤ 5 cm
 - 3 : L > 5 cm

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

- Small intestine :**
- R9 : proximal jejunum
 - R10 : distal jejunum
 - R11 : proximal ileon
 - R12 : distal ileon



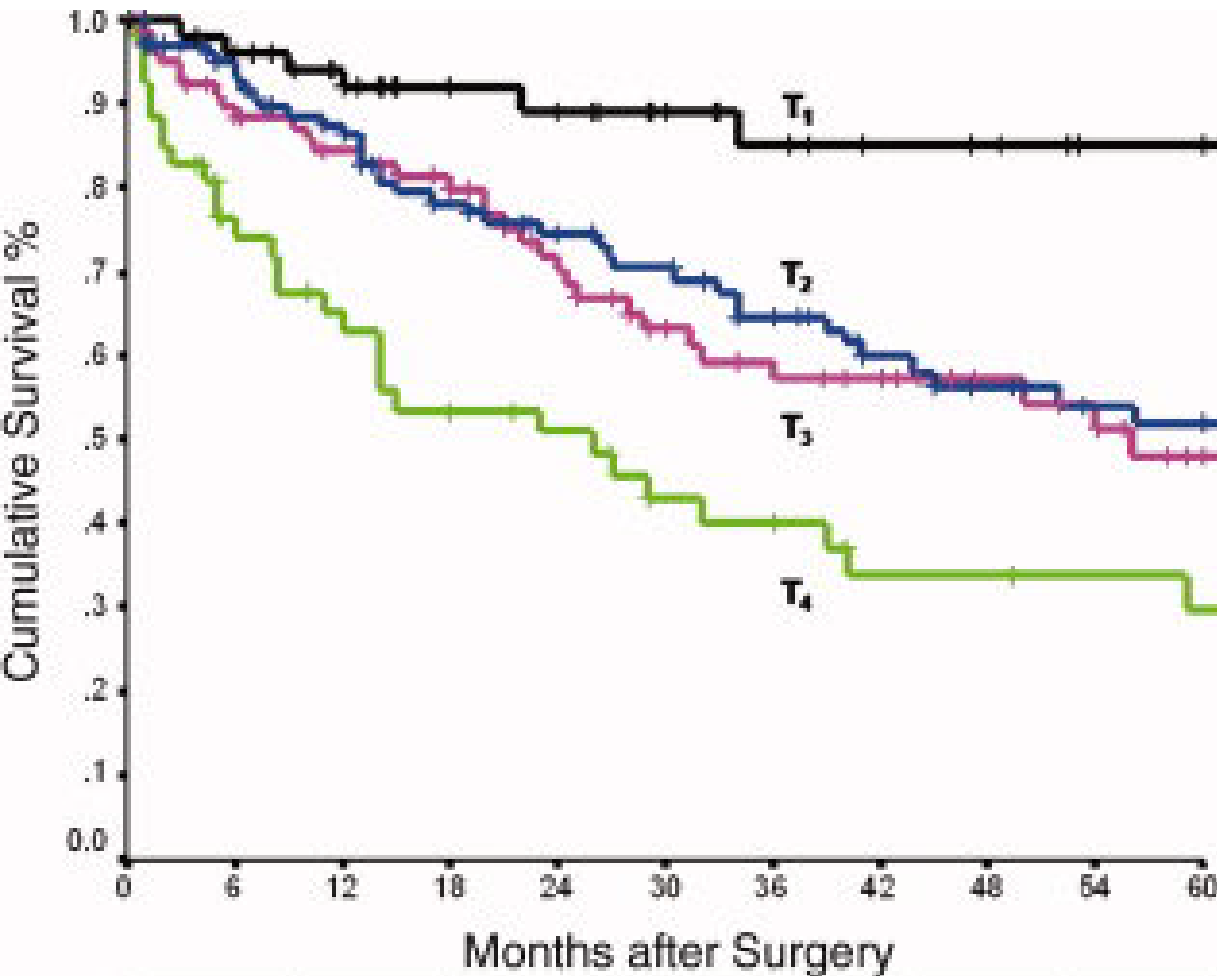
	Before surgery	After surgery
Region 0		
Region 1		
Region 2		
Region 3		
Region 4		
Region 5		
Region 6		
Region 7		
Region 8		
Region 9		
Region 10		
Region 11		
Region 12		
Total		

- 4 subgroups:
 T₁ (PCI 1-10)
 T₂ (PCI 11-20)
 T₃ (PCI 21-30)
 T₄ (PCI 30-39)

Gilly's classification

- **Stage 0** : no lesion (positive cytology)
- **Stage 1** : Malignant granulations less than 5mm in diameter, localized in one part of the abdomen
- **Stage 2** : Malignant granulations less than 5 mm in diameter, diffuse to the whole abdomen
- **Stage 3** : Localized or diffuse malignant granulations 5mm to 2 cm in diameter
- **Stage 4** : Localized or diffuse large malignant masses (more than 2 cm in diameter)

	Before surgery	After surgery



- T staging associated with significant difference in survival

T Stage	PCI	N	Median	1-year	3-year	5-year
T1	1-10	54	Notreached	92	85	85
T2	11-20	106	67	86	65	52
T3	21-30	81	58	84	57	40
T4	31-39	53	26	63	40	30

Completeness of Cytoreduction (CCR)

- **CCR** score quantifies the extent of residual disease present at the end of surgery into four categories
- **CCR-0**: no visible evidence of residual tumor
- **CCR-1**: residual tumors <2.5mm in diameter
- **CCR-2**: residual tumors between 2.5mm and 2.5cm
- **CCR-3**: residual tumors >2.5cm or a confluence of disease present at any site.

“Systemic therapy alone is no longer appropriate therapy for patients with limited peritoneal dissemination from a primary colorectal cancer”

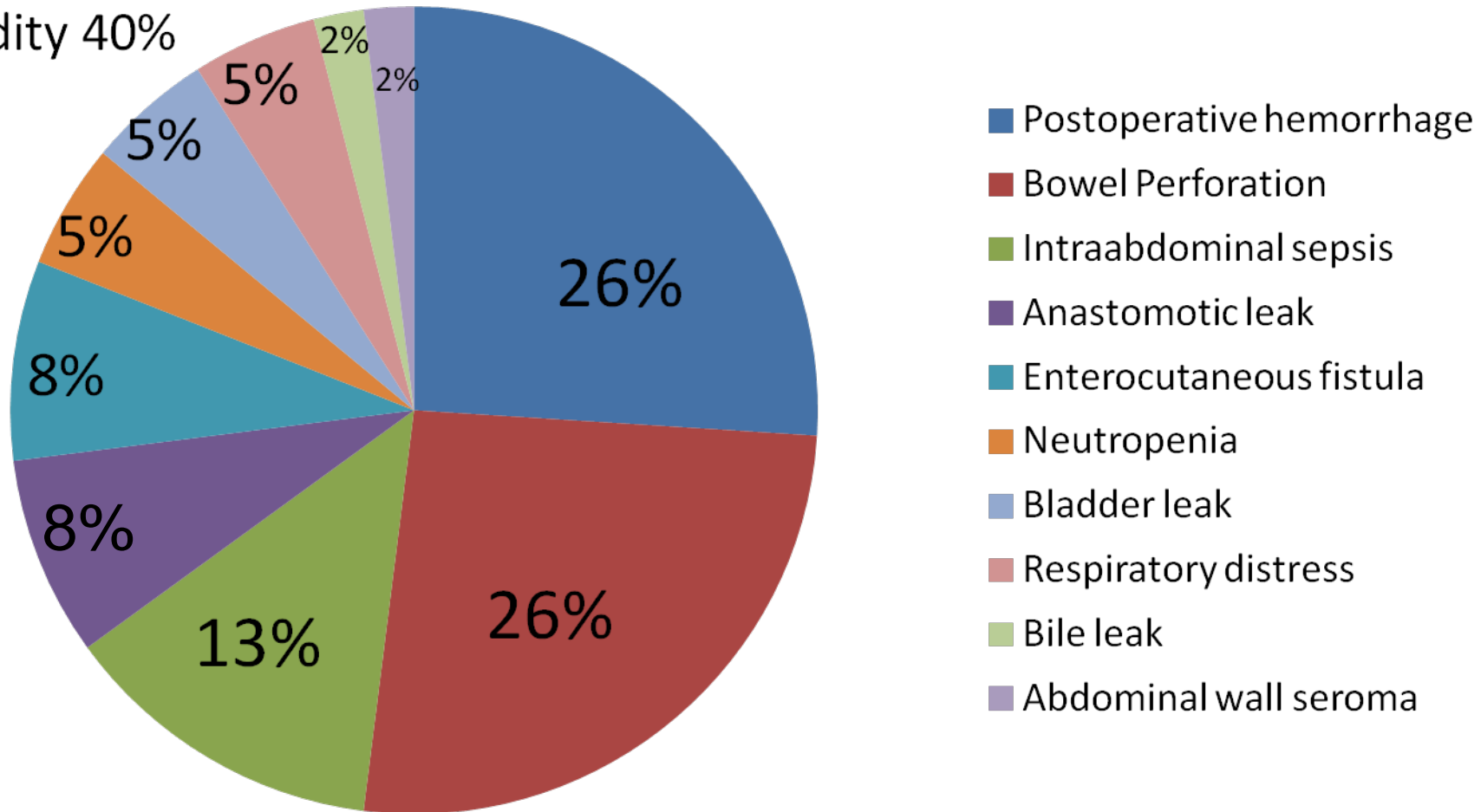
- Peritoneal Surface Malignancy Group determined 8 factors predictive of CCR
 - ECOG \leq 2
 - No evidence of extra-abdominal disease
 - \leq 3 small, resectable hepatic metastases
 - No biliary obstruction
 - No ureteral obstruction
 - No Bowel obstruction at > 1 site
 - SB involvement: Disease within mesentery with several sites of partial obstruction
 - Small volume disease in lesser omentum

What to expect

- Preop Evaluation
 - PE, Imaging, Surgical Path
- Bowel Prep
- OR
- Postop
 - Pain mgmt, ICU stay 2-3 dys, 12-14 days
hospital stay
- Recovery
 - 4to 8 wks

HIPEC Complications

Mortality 0-4%
Morbidity 40%



Carcinomatosis and Colorectal Cancer (CRC)

- 2nd most common site of CRC recurrence
- In recurrence, 10-35% is confined to peritoneum
- 10-15% of patients have peritoneal involvement at initial diagnosis
- Stage IV dz
 - I) Median survival
 - A) Systemic Chemo: 23 mths
 - B) By Metastatic site
 - WITH resection
 - Liver: 25-40 mths
 - Lung: 27-47 mths
 - Palliation
 - Peritoneum: 5-12 mths



CRC Metastasis Hepatectomy vs. CRS and HIPEC

(Cao et al. Journal of Surgical Oncology, 2009)

- Prospective study
 - 283 pts who underwent hepatectomy or peritonectomy (1995-2008)
 - Complete resections
 - No difference in median survival (37 mths)

Early involvement, a better chance

- Summary of current survival data of recent series in patients with CCR-0 resections
- Non-randomized trials

Author	Year	N	Median Survival (months)	3yr survival	5 yr survival
Morris	2005	30	30	62%	-
Elias	2005	30	60	53%	49%
Zoetmulder	2005	117	22	28%	19%
Sugarbaker	2005	70	33	44%	32%

Randomized Study of CRS + HIPEC

(Verwaal et al. Journal of Clinical Oncology , 2003)

Median Survival



Randomized Study of CRS + HIPEC

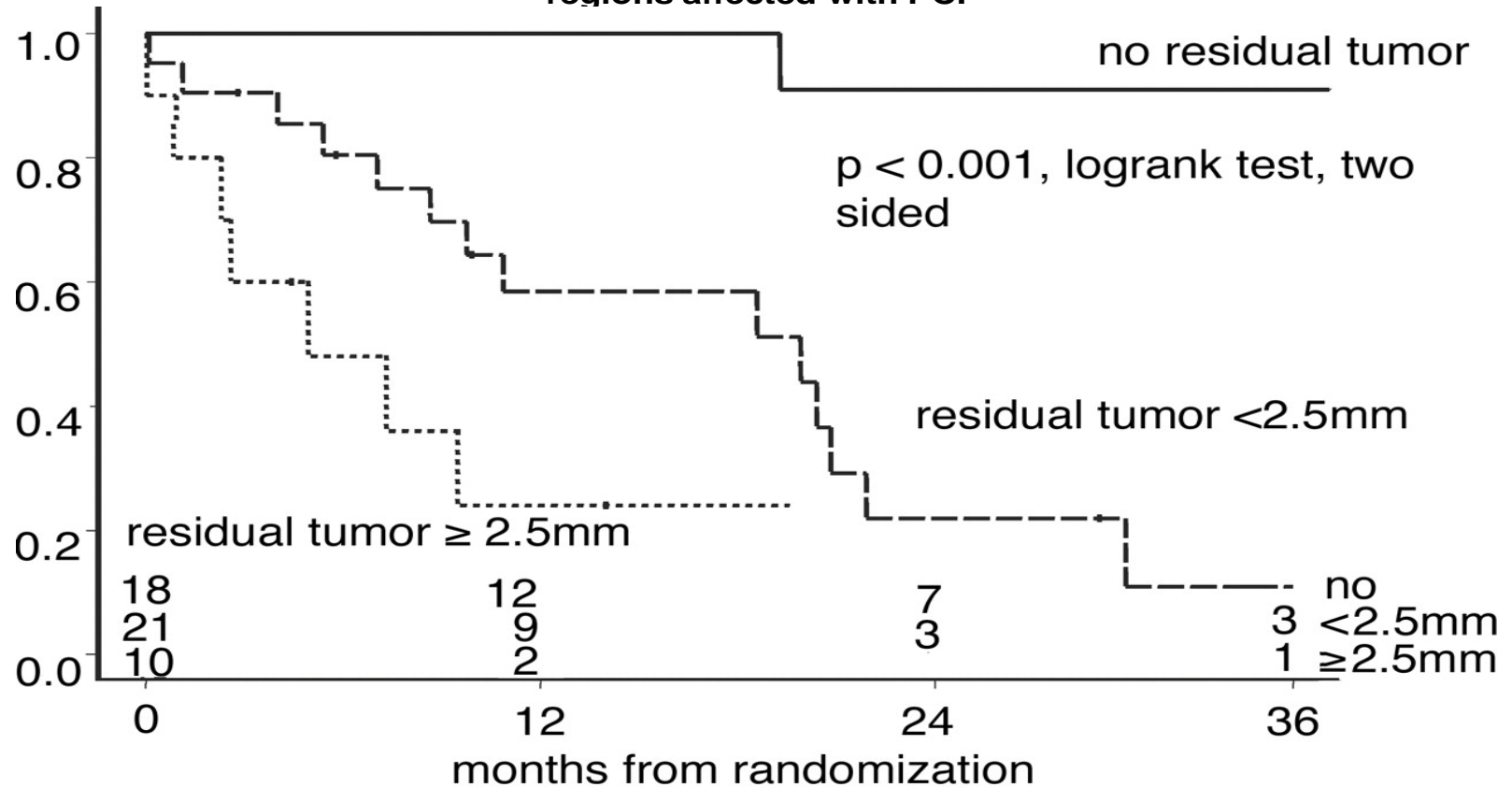
(Verwaal et al. Journal of Clinical Oncology , 2003)

- 8 % mortality
- 19% bone marrow toxicity
- 15% fistula rate
- Survival affected by extent of debulking
- Predicted 5yr OS for HIPEC arm is 20%

Survival by CCR

(Verwaal et al. Journal of Clinical Oncology , 2003)

Kaplan-Meier survival curve of 49 patients with peritoneal Carcinomatosis (PC) treated by cytoreduction followed by hyperthermic intraperitoneal chemotherapy, comparing the number of regions affected with PC.



Verwaal V J et al. JCO 2003;21:3737-3743

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At 8 yr follow-up...

- 90% of all events had occurred by this time
- Median progression free survival 7.7 mths vs. 12.6 mths
- Median disease specific survival 12.6 mths vs. 22.2 mths
- 48 mth median survival in CRS +HIPEC with CCR 1
- **45% 5 yr survival**

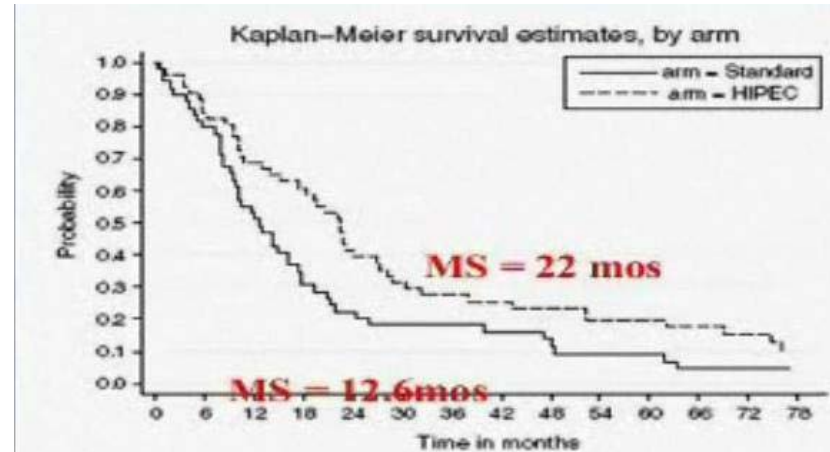


FIG. 2. Disease-specific survival of patients treated for peritoneal carcinomatosis, divided by treatment.

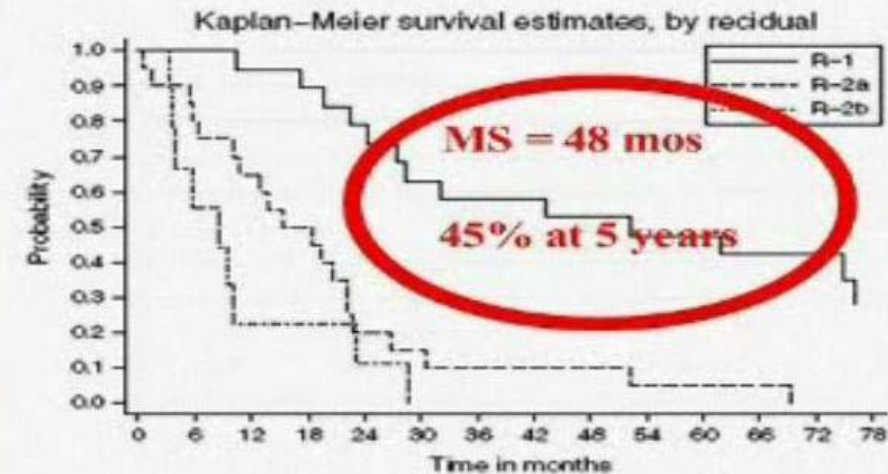
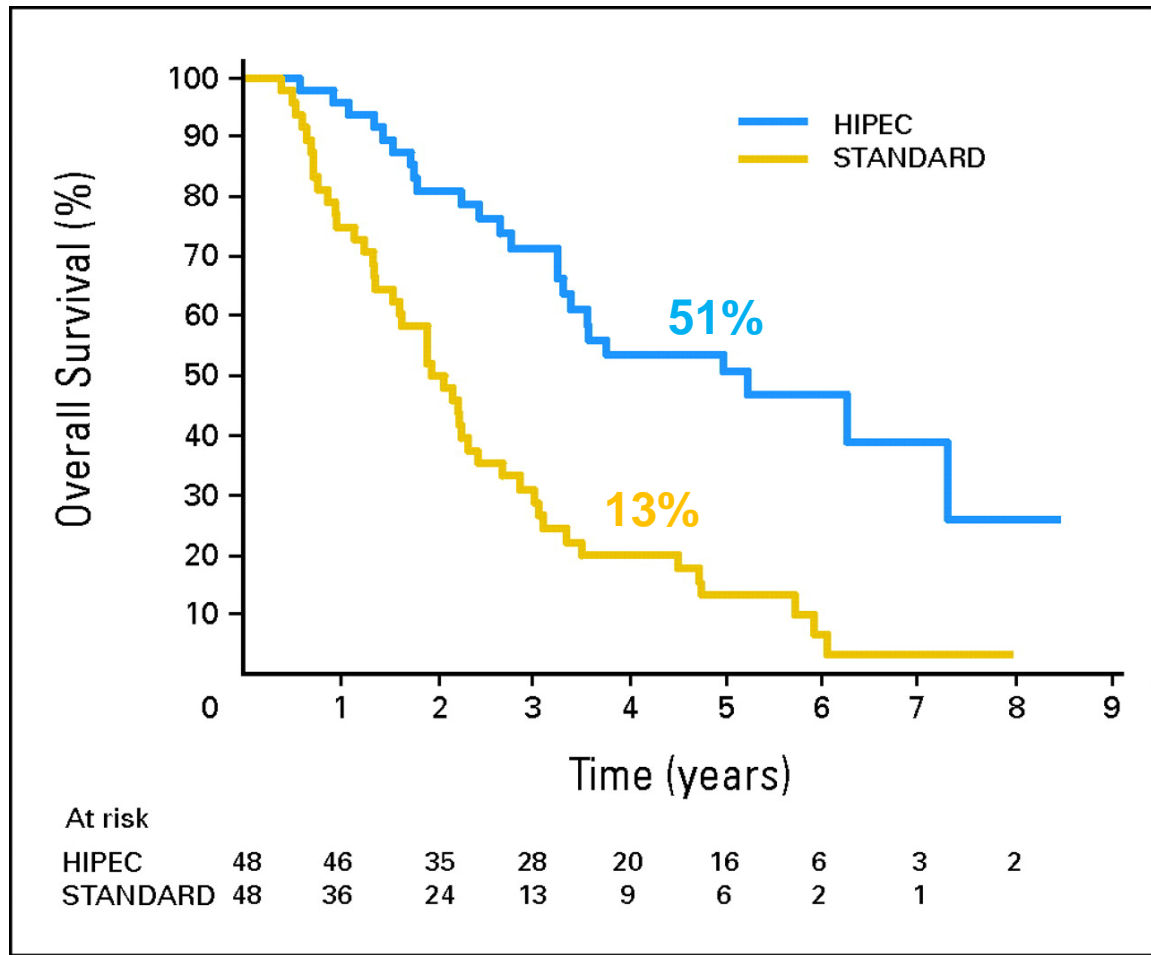


FIG. 3. Long-term results of cytoreduction followed by HIPEC in peritoneal carcinomatosis, divided to completeness of cytoreduction.



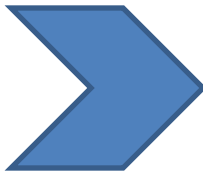
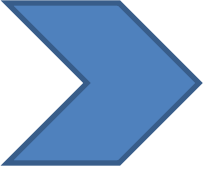
HIPEC with Contemporary Chemotherapy

(Elias et al. Journal of Clinical Oncology, 2009)



Median Survival: 23.9 mths (SC)
62.7 mths (CRS+ HIPEC)

Legit and covered....

- CRS + HIPEC is the standard of care of treatment for Mesothelioma and True Pseudomyxoma Peritonei
- Median Survival : 51 to 156 mths  Pseudomyxoma
- 5yr survival: 52-96%
- Median Survival: 34-92 mths  Mesothelioma
- 5yr survival: 29-59%

Conclusion

- Peritoneal Carcinomatosis is not necessarily a death sentence
- In high volume centers with experience in treating peritoneal malignancies, perioperative mortality is low
- HIPEC procedures result in a major improvement in overall survival compared to historical treatment with systemic therapy alone
- Most important factors in successful outcome:
 - Patient Selection (tumor burden)
 - Completeness of resection
 - Experience of the surgeon/center
 - Combination of treatments

References

- Cao CQ, Yan TD, Liauw W, Morris DL. Comparison of optimally resected hepatectomy and peritonectomy patients with colorectal cancer metastasis. *J Surg Oncol*. 2009 Dec 1;100(7):529-33
- Cotte, E, Passot, G, Mohamed, F, Vaudoyer, D, & Glehen, O. (2009). Management of peritoneal carcinomatosis from colorectal cancer. *The Cancer Journal*, 15(3), 243-248.
- Elias D, Lefevre JH, Chevalier J, Brouquet A, Marchal F, Classe JM, Ferron G, Guilloit JM, Meeus P, Goéré D, Bonastre J. Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. *J Clin Oncol*. 2009 Feb 10;27(5):681-5.
- Esquivel J, Sticca R, Sugarbaker P, Levine E, Yan TD, A et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the management of peritoneal surface malignancies of colonic origin: a consensus statement. *Ann Surg Oncol*. 2011 Dec;18 Suppl 3:334-5. No abstract available.
- Glockzin, G. (2009). Peritoneal carcinomatosis: patients selection, perioperative complications and quality of life related to cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *World Journal of Surgical Oncology*, 7(5).
- Gordon, PH, & Nivatvongs, S. (2007). *Principles and practice of surgery for the colon, rectum, and anus. Third edition*. New York: Informa Healthcare.
- Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. *Cancer Treatment Res*. 1996; 82: 359-374.
- Moran, B, Baratti, D, Yan, TD, Kusamura, S, & Deraco, M. (2008). Consensus statement on the loco-regional treatment of appendiceal mucinous neoplasms with peritoneal dissemination (pseudomyxoma peritonei). *Journal of Surgical Oncology*, 98, 277-282.
- Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: *Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group*. *Am J Clin Oncol* 5:649-655, 1982.
- Sadeghi B, Arvieux C, Glehen O, Beaujard AC, Rivoire M, Baulieux J, Fontaumard E, Brachet A, Caillot JL, Faure JL, Porcheron J, Peix JL, François Y, Vignal J, Gilly FN. Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. *Cancer*. 2000 Jan 15;88(2):358-63.
- Shen P, Thai K, Stewart JH, Howerton R, Loggie BW, Russell GB, Levine EA. Peritoneal surface disease from colorectal cancer: comparison with the hepatic metastases surgical paradigm in optimally resected patients. *Ann Surg Oncol*. 2008 Dec;15(12):3422-32.
- Sugarbaker PH. Peritonectomy procedures. *Ann Surg*. 1995 Jan;221(1):29-42
- Verwaal VJ, van Ruth S, de Bree E, van Sloothen GW, van Tinteren H, Boot H, Zoetmulder FA. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer... *J Clin Oncol*. 2003 Oct 15;21(20):3737-43.
- Verwaal VJ, Bruin S, Boot H, van Slooten G, van Tinteren H. 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer., *Ann Surg Oncol*. 2008 Sep;15(9):2426-32.
- Wolff, BG, Fleshman, JW, Beck, DE, Pemberton, JH, & Wexner, SD. (2007). *The ASCRS textbook of colon and rectal surgery*. New York: Springer.
- Yan TD, Black D, Savady R, Sugarbaker PH. A systematic review on the efficacy of cytoreductive surgery and perioperative intraperitoneal chemotherapy for pseudomyxoma peritonei. *Ann Surg Oncol*. 2007 Feb;14(2):484-92.
- Yan TD, Welch L, Black D, Sugarbaker PH. A systematic review on the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for diffuse malignancy peritoneal mesothelioma. *Ann Oncol*. 2007 May;18(5):827-34
- Yan TD, Deraco M, Elias D, Glehen O, Levine EA, Moran BJ, Morris DL, Chua TC, Piso P, Sugarbaker PH; Peritoneal Surface Oncology Group. A novel tumor-node-metastasis (TNM) staging system of diffuse malignant peritoneal mesothelioma using outcome analysis of a multi-institutional database. *Cancer*. 2010 Nov 18. [Epub ahead of print]