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

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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 hemicolecotomy
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 (T_4N_1M_1)
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!!!
Definitions

• 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?

Gastric, Pancreatic, Small Bowel, Gallbladder
Colorectal
Ovarian
Appendiceal
Pseudomyxoma
Breast
Mesothelioma
## Scope of the Problem

<table>
<thead>
<tr>
<th>Condition</th>
<th># of patients</th>
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<tbody>
<tr>
<td>Gastric, Pancreatic, Small Bowel, Gallbladder</td>
<td>20,000</td>
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<tr>
<td>Colorectal</td>
<td>23,000</td>
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<tr>
<td>Ovarian</td>
<td>18,000</td>
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<tr>
<td>Appendiceal</td>
<td>1,200</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>&lt;1,000</td>
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</table>

- 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
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)

<table>
<thead>
<tr>
<th>ECOG PERFORMANCE STATUS*</th>
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<tr>
<td><strong>Grade</strong></td>
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Oken et al, J Clin Oncol 1982
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°C
- Open abdomen and irrigate
### Peritoneal Cancer Index (PCI) de Sugarbaker

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

<table>
<thead>
<tr>
<th>Region</th>
<th>Before surgery</th>
<th>After surgery</th>
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<tbody>
<tr>
<td>0</td>
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<tr>
<td>Total</td>
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</table>

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

### 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)

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</tbody>
</table>

4 subgroups:
- $T_1$ (PCI 1-10)
- $T_2$ (PCI 11-20)
- $T_3$ (PCI 21-30)
- $T_4$ (PCI 30-39)
PCI impacts survival

- T staging associated with significant difference in survival

Sugarbaker et al, Cancer, 2010
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 ≤ 2
  - No evidence of extra-abdominal disease
  - ≤ 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
  - 4 to 8 wks
HIPEC Complications

Mortality 0-4%
Morbidity 40%

- Postoperative hemorrhage: 26%
- Bowel Perforation: 13%
- Intraabdominal sepsis: 8%
- Anastomotic leak: 8%
- Enterocutaneous fistula: 5%
- Neutropenia: 5%
- Bladder leak: 5%
- Respiratory distress: 2%
- Bile leak: 2%
- Abdominal wall seroma: 2%
Carcinomatosis and Colorectal Cancer (CRC)

- 2\textsuperscript{nd} 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

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>Median Survival (months)</th>
<th>3yr survival</th>
<th>5 yr survival</th>
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<td>30</td>
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<tr>
<td>Elias</td>
<td>2005</td>
<td>30</td>
<td>60</td>
<td>53%</td>
<td>49%</td>
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<tr>
<td>Zoetmulder</td>
<td>2005</td>
<td>117</td>
<td>22</td>
<td>28%</td>
<td>19%</td>
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<tr>
<td>Sugarbaker</td>
<td>2005</td>
<td>70</td>
<td>33</td>
<td>44%</td>
<td>32%</td>
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</table>
Randomized Study of CRS + HIPEC
(Verwaal et al. Journal of Clinical Oncology, 2003)

105 patients with carcinomatosis from CRC

- Standard Chemotherapy and Palliative Surgery: 12.6 months
- CRS + HIPEC and Standard Chemotherapy: 22.3 months
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%
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.

- No residual tumor: 18 patients
- Residual tumor ≥ 2.5mm: 21 patients
- Residual tumor <2.5mm: 10 patients

-with p < 0.001, logrank test, two sided

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

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
- 5yr survival: 52-96%
- Median Survival: 34-92 mths
- 5yr survival: 29-59%

Yan & Sugarbaker, Ann Oncol, 2007
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