Update on Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Peritoneal Carcinomatosis

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October 22, 2011
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
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
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
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?
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?
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 adenomucinosi implies benign disease
- Life-threatening, uniformly fatal disease without treatment
- Newer classification
  
  low grade adenocarcinoma
  
  high grade adenocarcinoma

Rare?

• National pathologic database study - Netherlands


• 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

EJSO 2008;34(2):196-201
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)

Ann Surg 2005;241:300-308
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

JCO 1988;6;106-118 Cancer 2000;88:358-63
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

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

Lesion Size Score
LS 0 - no tumor seen
LS 1 <5mm
LS 2 - 5 mm-5cm
LS 3 > 5cm/ confluent
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

Adv Surg 1996:30;233-280
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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Synergism</th>
<th>Cell-cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitomycin C</td>
<td>Yes - 39°C</td>
<td>Yes</td>
</tr>
<tr>
<td>Cisplatinum</td>
<td>Yes 39°C</td>
<td>Yes</td>
</tr>
<tr>
<td>Melphalan</td>
<td>Yes - 39°C</td>
<td>Yes</td>
</tr>
<tr>
<td>Mitroantrone</td>
<td>Yes 39°C</td>
<td>Yes</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>Yes - 39°C</td>
<td>Yes</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Yes -42°C</td>
<td>Yes</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>5 FU</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

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 (EPI PC) 5FU X 5 days

- **February 2008-June 2009 (Protocol 2)**
  - 65 consecutive patients with new protocol (now≈164)
    - CS + HIPEC (oxaliplatin) + IV 5FU

## Accrual Pattern / Pathologic Diagnoses

<table>
<thead>
<tr>
<th>Site</th>
<th>Count</th>
</tr>
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<tbody>
<tr>
<td>Appendix</td>
<td>159</td>
</tr>
<tr>
<td>Colon/Rectum</td>
<td>79</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>10</td>
</tr>
<tr>
<td>Primary Peritoneum</td>
<td>7</td>
</tr>
<tr>
<td>Small Bowel</td>
<td>5</td>
</tr>
<tr>
<td>Ovary</td>
<td>2</td>
</tr>
<tr>
<td>Stomach</td>
<td>3</td>
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</table>

### Number of patients undergoing cytoreduction surgery

<table>
<thead>
<tr>
<th>Year</th>
<th>Count</th>
</tr>
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<tbody>
<tr>
<td>2000</td>
<td>265</td>
</tr>
<tr>
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<td>2008</td>
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<tr>
<td>2009</td>
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</tr>
<tr>
<td>2010</td>
<td></td>
</tr>
<tr>
<td>2011</td>
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</table>
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 + EPI PC (early protocol)

Ann Surg Oncol 2010;17:Suppl
### Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Median/Range)</td>
<td>52 / 18-79</td>
</tr>
<tr>
<td>Sex (Female/Male)</td>
<td>90 / 76</td>
</tr>
<tr>
<td>LOS (Mean/Range)</td>
<td>23 / 5-59</td>
</tr>
<tr>
<td>PCI Score (Mean/Range/Mode)</td>
<td>21/0-39/39</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Residual Disease (CC 0/1/2-3)</td>
<td>139 / 8 / 19</td>
</tr>
<tr>
<td>Operative Time in Minutes (Mean/Range)</td>
<td>380 / 63-690</td>
</tr>
<tr>
<td>Estimated Blood Loss in mL (Mean/Range)</td>
<td>1190 / 0-4800</td>
</tr>
<tr>
<td>Red Blood Cells in Units (Mean/Range)</td>
<td>1 / 0-17</td>
</tr>
<tr>
<td>ICU Admission Post-op (%)</td>
<td>35</td>
</tr>
</tbody>
</table>
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)

Am J Surg 2011;201:645-9
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 EPIPC due to complications
First Protocol (HIPEC + EPIC) vs. Second Protocol (HIPEC + IV5FU)

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

- 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

Ann Surg Oncol 2010;17 (Suppl 1):S8
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%

Am J Surg 2011;201:645-9
Disease-Free Survival

p=0.006

Percent survival vs Time (months)

Appendix

Colorectal
Overall Survival

![Graph showing overall survival rates for Appendix and Colorectal conditions with a p-value of 0.0005.](chart.png)
Summary - Appendix

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

<table>
<thead>
<tr>
<th></th>
<th>3-year</th>
<th>5-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS</td>
<td>48%</td>
<td>42%</td>
</tr>
<tr>
<td>OS</td>
<td>76%</td>
<td>62%</td>
</tr>
</tbody>
</table>
Summary - Colorectal

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

<table>
<thead>
<tr>
<th></th>
<th>3-year</th>
<th>5-year</th>
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</thead>
<tbody>
<tr>
<td>DFS</td>
<td>34%</td>
<td>26%</td>
</tr>
<tr>
<td>OS</td>
<td>38%</td>
<td>34%</td>
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</table>
# Comparison of Long-term Results

## Table 1  Comparison of long-term results: appendix

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>MFU, mo</th>
<th>3-y DFS, %</th>
<th>3-y OS, %</th>
<th>5-y DFS, %</th>
<th>5-y OS, %</th>
<th>NED</th>
<th>AWD</th>
<th>DWD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Study</td>
<td>58</td>
<td>32</td>
<td>48</td>
<td>76</td>
<td>42</td>
<td>62</td>
<td>45</td>
<td>21</td>
<td>34</td>
</tr>
<tr>
<td>Zoetmulder</td>
<td>103</td>
<td>52</td>
<td>44</td>
<td>71</td>
<td>37</td>
<td>60</td>
<td>61</td>
<td>20</td>
<td>19</td>
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<tr>
<td>Sugarbaker</td>
<td>501</td>
<td>48</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>47</td>
<td>15</td>
<td>32</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>MFU, mo</th>
<th>3-y DFS, %</th>
<th>3-y OS, %</th>
<th>5-y DFS, %</th>
<th>5-y OS, %</th>
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</thead>
<tbody>
<tr>
<td>Current Study</td>
<td>31</td>
<td>25</td>
<td>34</td>
<td>38</td>
<td>26</td>
<td>34</td>
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<tr>
<td>Zoetmulder</td>
<td>117</td>
<td>22</td>
<td>-</td>
<td>28</td>
<td>-</td>
<td>19</td>
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<tr>
<td>Glehen et al.</td>
<td>506</td>
<td>53</td>
<td>16</td>
<td>39</td>
<td>10</td>
<td>19</td>
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<tr>
<td>Elias et al.</td>
<td>523</td>
<td>45</td>
<td>-</td>
<td>-</td>
<td>10</td>
<td>27</td>
</tr>
</tbody>
</table>

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)

Am J Surg. 2011;201;645-9
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

J Clin Oncol 2003;21:3737-43
Survival Analysis

22.3 m vs. 12.6 m

p = 0.032, logrank test, two-sided

J Clin Oncol 2003;21:3737-43
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%

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
Learning Questions

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c) Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC)

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• Options?
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%

World J Gastroenterol 2004;10:2727-30

J Surg Oncol 2008;98:273-76
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

Cochr Database Syst Rev 2006