Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC): Now and the Future

Mazin Al-kasspooles, MD
Associate Professor of Surgery
Division of Surgical Oncology
Director, Regional Therapy Program
University of Kansas Medical Center

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Peritoneal Surface Malignancy

- **Definition**
  - Cancerous cells that have “seeded” outside the primary site of cancer and formed tumors on:
    - Peritoneal surfaces
      - Inside of the abdominal and pelvic walls
    - Surfaces of the bowel, including the mesentery
    - Omentum
    - On surfaces of other organs:
      - Liver, Spleen, Gallbladder, Bladder, Uterus, Ovaries
  - **Different than cancer that has spread by lymphatics or the blood stream.**

- **Aggressive Disease Process**
  - Historically considered a highly terminal process with very few patients surviving over 6 months, even when treated with systemic therapy
Peritoneal Surface Malignancy
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Pathophysiology of Peritoneal Malignancy

• **Mechanisms of Peritoneal Seeding**
  – Free intraperitoneal seeding from serosal invasion
  – Spontaneous or iatrogenic tumor perforation through serosa
  – Late site of metastases in advanced cases
    • Via bloodstream or lymphatics
  – Loss of blood or tissue fluid containing tumor cells into the surgical field
    • Veins
    • Lymphatics
Appendiceal Neoplasm Prior to Rupture
Pathophysiology of Peritoneal Malignancy

- **Patterns of dissemination**
  - Gutters of the abdomen and pelvis
    - GRAVITY!
  - Areas that are relatively immobile
    - Often see “sparing“ of the small bowel

- **Survival in micro-environment**
  - Evade immune system
  - Develop blood supply

- **Growth**
  - Using bodies own inflammatory/recovery process
  - Angiogenesis

- **Self-sustaining**
  - Peritoneal tumors block absorption of fluid → ascites
  - Ascites provides fertile environment for tumor progression
Rationale for Intraperitoneal Chemotherapy

- Systemic Chemotherapy relatively ineffective for this disease process

- Paradoxically, surgery alone favors peritoneal dissemination
  - Tumor spillage
  - Tissue trauma
    - Environment conducive to tumor implantation and growth
# Hyperthermic Intraperitoneal Chemotherapy

## Rationale

### Direct Effects of Hyperthermia

<table>
<thead>
<tr>
<th>Effect</th>
<th>Malignant cell tissue</th>
<th>Normal cell tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell death (41–43°C)</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Cell respiration</td>
<td>decreased oxidative metabolism</td>
<td>normal</td>
</tr>
<tr>
<td>RNA synthesis</td>
<td>inhibited (reversible)</td>
<td>inhibited (reversible)</td>
</tr>
<tr>
<td>Mitosis</td>
<td>arrested (reversible)</td>
<td>arrested (reversible)</td>
</tr>
<tr>
<td>Lysosomes (#)</td>
<td>increased</td>
<td>slight increase or nl.</td>
</tr>
<tr>
<td>Lysosome lability</td>
<td>increased</td>
<td>normal</td>
</tr>
<tr>
<td>Microcirculation</td>
<td>decreased flow</td>
<td>increased flow</td>
</tr>
<tr>
<td>Microenvironment</td>
<td>lactic acid, low pH</td>
<td>minimal change</td>
</tr>
</tbody>
</table>
Hyperthermic Intraperitoneal Chemotherapy

*Rationale*

Advantages of Adding Hyperthermia to Chemotherapy

<table>
<thead>
<tr>
<th>Advantages of hyperthermia in treatment of malignancy</th>
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<tbody>
<tr>
<td><strong>General</strong></td>
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<tr>
<td>Selective cytotoxic effect for malignant cells</td>
</tr>
<tr>
<td>Minimal toxicity for normal tissue ( &lt; 45°C)</td>
</tr>
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<td>Potentiation of other therapies (radiotherapy, chemotherapy)</td>
</tr>
<tr>
<td>Stimulation of host immune system</td>
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<tr>
<td><strong>With chemotherapy</strong></td>
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<tr>
<td>Increased cytotoxicity of chemotherapeutic agents</td>
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<tr>
<td>Increases drug penetration into tissue</td>
</tr>
<tr>
<td>Increased membrane permeability</td>
</tr>
<tr>
<td>Inhibition of repair mechanisms</td>
</tr>
<tr>
<td>Temperature-dependent increases in drug action</td>
</tr>
<tr>
<td>Overcome drug resistance</td>
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</tbody>
</table>
Indication for Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (CRS-HIPEC)

- **Perforated Appendiceal Cancer**
  - Standard of care for 3 decades
  - Classic “jelly-belly” (pseudomyxoma peritonei)
  - Approximately 1000 cases per year and stable

- **Primary Peritoneal Mesothelioma**
  - Mesothelioma that originates from inside the abdomen
  - Standard of care for 3 decades
  - Approximately 500 cases per year and stable
Indication for Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (CRS-HIPEC)

- **Abdominal Recurrence of Colorectal Cancer (Carcinomatosis)**
  - CRS-HIPEC utilized in past 10 years
    - Data shows that survival is doubled with complete cytoreduction
  - Use for this disease rapidly increasing
  - *Approximately 20,000 cases per year and increasing*

- **Recurrent Ovarian Cancer**
  - CRS-HIPEC utilized in past 3 years
    - Data shows that survival is doubled with complete cytoreduction
  - Use for this disease rapidly increasing
  - *Approximately 20,000 cases per year and increasing*
Volume at the University of Kansas Medical Center

Total Evaluated in Operating Room for HIPEC

- 2011: 16
- 2012: 22
- 2013: 60
- 2014: 61
Fig. 1. Modified lithotomy position.
Fig. 2. Self-retaining retractor and elliptical incision.
Fig. 3. Centripetal surgical dissection of the parietal peritoneum from the inferior surface of the anterior abdominal wall.
Fig. 5. Parietal peritoneal dissection to the paracolic sulcus and beyond.
Fig. 6. Left subphrenic peritoneectomy.
Fig. 7. Greater omentectomy and splenectomy with completion of the left subphrenic peritoneectomy.
Fig. 8. Peritoneal stripping from beneath the right hemidiaphragm and electroevaporation of tumor from the surface of the liver.
Fig. 9. Removal of an envelope of tumor from beneath the right hemidiaphragm from the right subhepatic space and from the surface of the liver.
Fig. 10. Completed right subphrenic peritonectomy.
Fig. 11. Cholecystectomy with stripping of the hepatoduodenal ligament.
Fig. 12. Circumferential resection of the hepatogastric ligament and lesser omentum by digital dissection.
Fig. 13. Limits of the lesser omentectomy with stripping of the omental bursa.
Fig. 14. Stripping of the floor of the omental bursa.
Fig. 15. Lesser omentectomy and omental bursectomy completed.
Fig. 16. Limits of the complete pelvic peritonectomy.
Fig. 17. Resection of the rectosigmoid colon, uterus, and cul-de-sac of Douglas.
Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

- Insertion of cannulas and temp. probes
- “Temporary” close
- Connect circuit to Pump
- Circulate and heat for 30 to 90 minutes (depends on drug) at 41 - 43 degrees Celsius
- Open and irrigate
- Reconstructive surgery & close
Future Trends

• **Almost exponential rise in the CRS-HIPEC procedure**
  – Indications continue to broaden
  – Increased awareness of potential candidates
    • e.g. Education of medical oncologists and general surgeons
  – Increased number of candidates for given disease site
    • Older population
    • Patients living longer with advanced cancer

• **Discovery of more effective drug combinations to be used in perfusate**

• **Discovery of new novel agents to be used in perfusate**

• **Better delivery mechanisms**
  – Use of nanoparticles that can “linger” in the abdominal cavity after CRS-HIPEC

• **Improved patient selection**
  – Not all candidates benefit from the procedure
    • Preoperative clinical information (scoring system)
    • Molecular markers
Opportunities at KUMC

Geographical Considerations