Peritoneal Surface Malignancy
Relauching OHSU’s HIPEC Program

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Divya Sood, MD
Assistant Professor of Surgery, Surgical Oncology
Director of Peritoneal Surface Malignancy Program
Disclosures

• None
Agenda

• Overview of Peritoneal Surface Malignancies and HIPEC
• MythBusters – PSM Edition
• Active Areas of Investigation
• OHSU’s PSM/HIPEC Program
Peritoneal Surface Malignancy

• Broad and heterogeneous group of diseases

• Pathophysiology complex and not fully understood
  – Mesothelial transformation (primary)
  – Shedding and implantation (secondary)

• Diagnosis is challenging, often requires direct visualization (laparoscopy/laparotomy)
Intraperitoneal Therapies (with or without Cytoreduction)

- HIPEC: Hyperthermic Intraperitoneal Chemotherapy
- NIPS: Neoadjuvant Intraperitoneal and Systemic Chemotherapy
- PIPAC: Pressurized Intraperitoneal Aerosol Chemotherapy
- EPIC: Early Postoperative Intraperitoneal Chemotherapy
PSM Myth #1: PSM is a Rare Disease
Epidemiology

• GLOBOCAN Registry does not designate PSM: don’t have an exact incidence of PSM
  – Most data comes from western/high income cohort samples
• Labeled an orphan disease – limits funding
• Actually incredibly common
  – Autopsy studies suggest upwards of 20% of solid organ cancer patients dying with peritoneal metastases present (despite NCCN single digit incidences)
  – Colorectal cancer is 2nd most cancer: 5-8% synchronous, another 5-12% metachronous PSM
  – Ovarian cancer: 60-70% develop PSM
• Long list of other cancers
Epidemiology

Secondary extraperitoneal origin
- Lung cancer
- Breast cancer
- Kidney cancer
- Malignant melanoma

Peritoneal cavity

Primary peritoneal origin
- Peritoneal mesothelioma
- Primary peritoneal cancer

Secondary intraperitoneal origin
- Cholangiocarcinoma
- Gastric cancer
- Pancreatic cancer
- Colorectal cancer
- Small bowel cancer
- Ovarian cancer
- Endometrial cancer
- Appendiceal cancer
- Sarcoma
PSM Myth #2: PSM is incurable
Stigma and Nihilism
Long Term Survival

• Subset of patients in almost every disease site
Long Term Survival

• CRC
  – Median survival with CRS/HIPEC 40-60 months
  – 16% 10-year survival; increased to 40% if PCI<10
• Ovarian
  – Median survival 40-70 months
• Appendiceal Adenocarcinoma
  – 3-10 years median survival
  – >20 year for LAMN
Long Term Survival

• Those who get complete cytoreduction do better (refer early!)
• Long-term survival is an appropriate goal of care and a valid endpoint for clinical trials
PSM Myth 13: Systemic Therapy is Standard of Care
Systematic Exclusion from Clinical Trials

Number of Patients

45113

670

Peritoneal Metastases

Other Metastases
Standard of Care for PSM?

- Upfront CRS for CRC is standard in several countries
- Mixed in the US (Chicago Consensus Guidelines gives options of CRS/HIPEC alone, before, or after chemotherapy)
- Median survival 16 months on systemic vs >40 months after complete CRS/HIPEC...refer early!
  - CAIRO6 first to study systemic chemo in this population
PSM Myth #4: Biology is King
Candidacy for Oligometastatic Approach

1. Performance status/tolerability of surgery
2. Burden of disease/PCI/resectability
3. Tumor biology...but what does this mean in PSM?
   - Site of primary
   - LAMN vs adenocarcinoma
   - Grade/differentiation
   - High risk path features (LVI, PNI, LN+, signet rings, goblet cells, etc)
36 year old woman
LAMN with PMP

62 year old man
Pancreatic adenocarcinoma
- Patient selection is still a question mark
- Who are we hurting and who are we missing?
- What do we do next?
Active Areas of Research

- Microbiome and diet/metabolomics
- Precision oncology
- Detection and surveillance
- Quality of life
- Surgical clinical trials
<table>
<thead>
<tr>
<th>CANCER THERAPY TYPE</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>5-Flourouracil</td>
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<td></td>
<td>Carboplatin</td>
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<tr>
<td>Hormone therapy</td>
<td>Abiraterone acetate</td>
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<td></td>
<td>Fulvestrant</td>
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<td>Epigenetic modifiers</td>
<td>Azaclitidine</td>
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<td></td>
<td>Decitabine</td>
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<td>Immune stimulators &amp; Checkpoint inhibitors</td>
<td>Aldesleukin</td>
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<tr>
<td></td>
<td>Pembrolizumab</td>
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<tr>
<td>Angiogenesis inhibitors</td>
<td>Bevacizumab</td>
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<td></td>
<td>Regorafenib</td>
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<tr>
<td>Vaccines</td>
<td>Sipuleucel-T</td>
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<td></td>
<td>DCVax-L</td>
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<tr>
<td>Adoptive immunotherapy</td>
<td>Anti-CD19 CAR-T cell therapy</td>
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<tr>
<td></td>
<td>CART-Meso</td>
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<tr>
<td>Therapeutic antibodies</td>
<td>Cetuximab</td>
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<td></td>
<td>TDM-1</td>
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<tr>
<td>Cell signaling inhibitors</td>
<td>Ibrutinib</td>
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<td></td>
<td>Imatinib</td>
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<td>Ceritin</td>
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Within each category, some therapeutics are more precise than others.

Precision
<table>
<thead>
<tr>
<th>Class of immunotherapy</th>
<th>Oncolytic virus</th>
<th>Anti-CTLA4</th>
<th>Anti-PD1</th>
<th>Adoptive cell therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Lysed tumour cell</td>
<td>CD8⁺ T cell</td>
<td>Progenitor PD₁⁺CD8⁺ T cell</td>
<td>CAR T cell</td>
</tr>
<tr>
<td><strong>Periphery</strong></td>
<td>Prime new T cells (via tumour lysis)</td>
<td>Enhance T cell priming</td>
<td>Enhance T cell differentiation</td>
<td>Bypass priming, Augment immunity</td>
</tr>
<tr>
<td><strong>Metabolic barriers</strong></td>
<td>Initial activation of T cells requires metabolic intermediates</td>
<td>Access to nutrients critical immediately after activation. CTLA4 ligation inhibits glycolysis upregulation during activation</td>
<td>Intrinsic T cell signaling may limit nutrient sensing. PD1 ligation shifts T cells to FAO, not glycolysis, during activation</td>
<td>Hyperglycaemic media, Reduced tumour control</td>
</tr>
</tbody>
</table>

**TME**

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Lyse tumour cells and inflame the TME</th>
<th>Inhibit Treg cells</th>
<th>Induce differentiation</th>
<th>Infiltrate and lyse tumour cells</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metabolic barriers</strong></td>
<td>Low O₂ level, Sufficient O₂</td>
<td>Lactate</td>
<td>Low O₂ and αKG levels</td>
<td>Glucose within the TME, Hypoxia prevents infiltration</td>
</tr>
<tr>
<td><strong>Depaux Nat Rev Immunol Apr 2021</strong></td>
<td>Hypoxia inhibits (some) viral replication and spread, Hypoxia prevents infiltration</td>
<td>Glycolytic tumour, Suppression of glycolysis, Upregulation of OXPHOS</td>
<td>O₂, αKG needed for epigenetic remodelling</td>
<td>Competition for glucose within the TME, Hypoxia prevents infiltration</td>
</tr>
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Detection
Active Areas of Research

• Microbiome and diet/metabolomics
• Precision oncology
• Detection and surveillance
• Quality of life
• Surgical clinical trials
Comprehensive PSM Program at OHSU Knight Cancer Institute
HIPEC Surgery

Dr. Divya Sood is a cancer surgeon and researcher with advanced expertise in HIPEC surgery.

HIPEC surgery is a leading-edge therapy for patients whose cancer has spread inside the abdomen. Key points to know about this therapy:
Caring for PSM Patients

- Hematologic impacts
- Malnutrition
- Physical deconditioning
- Psychological recovery
- Fertility
- Sexual function
- Bowel/bladder function
- Failure to thrive
Big Problems :: Big Team
GOALS:
• Improve survival and oncologic outcomes
• Reduce LOS, debility, dependence
• Increase patient satisfaction
• Improve QOL and perioperative outcomes
• Increase clinical trial participation
# Impact of a Comprehensive Program

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<tr>
<th>Metric</th>
<th>OHSU</th>
<th>Benchmark High Volume Programs</th>
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<tbody>
<tr>
<td>Volume</td>
<td>Bases off 2 months - projected to have &gt;40 in first year</td>
<td>100/year (3 surgeons)</td>
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<tr>
<td>Median LOS</td>
<td>5 days</td>
<td>10 days</td>
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<tr>
<td>30-day mortality</td>
<td>0%</td>
<td>4.9%</td>
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<tr>
<td>ICU admission</td>
<td>0%</td>
<td>38%</td>
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Final Thoughts

- PSM is a common but heterogeneous group of diseases
- Long-term survival is a realistic goal for this population
- Early referral for consideration of surgery improves outcomes
- Patient selection is key, but still a work in progress
- There are exciting areas of investigation in the pipeline
- A comprehensive multidisciplinary team approach is critical to support PSM patients
Thank You

soodd@ohsu.edu
@DivyaSoodMD