Colorectal Cancer in The Abdomen

Oliver Eng, MD, FACS, FSSO
Associate Professor of Surgery
Associate Director, Peritoneal Surface Malignancy Program
Associate Program Director, Complex General Surgical Oncology Fellowship
Co-Director, Student Clerkship
Vice Chair, Protocol Review and Monitoring Committee, Chao Family Comprehensive Cancer Center
Disclosures

- Speaker, Tempus Labs., Inc.
- Medical Advisory Board, Verywell Health/Health.com
Colorectal Cancer

- 3rd most common cancer diagnosed in the United States


Siegel et al, CA Cancer J Clin, 2023
Colorectal Cancer that Has Spread - Metastasis

- Management has evolved over the past several decades

- Concept of "Metastasectomy"
  
  *Arch. Surg. 1997—"Hepatic Resection for Metastatic Colorectal Cancer Results in Cure for Some Patients"

- Reduction of Disease Burden → Resectability → Survival

*Jamison et al, Arch Surg 1997*
Abdomen - Peritoneum
Abdomen - Peritoneum

- Imaging under-representation

- Limited in detection <1cm diameter

- Imaging correctly predicted disease burden in 50% of patients

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Table 4
Inter-rater agreement (κ) between radiologists 1 and 2 for DW-MRI and CT for sites of disease.

<table>
<thead>
<tr>
<th>Location</th>
<th>DW-MRI (κ)</th>
<th>CT (κ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omentum</td>
<td>0.899</td>
<td>0.458</td>
</tr>
<tr>
<td>Gastrohepatic ligament</td>
<td>0.316</td>
<td>0.000</td>
</tr>
<tr>
<td>Morrison’s pouch</td>
<td>0.683</td>
<td>0.182</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.038</td>
<td>0.040</td>
</tr>
<tr>
<td>Liver parenchyma</td>
<td>0.646</td>
<td>0.649</td>
</tr>
<tr>
<td>Liver surface</td>
<td>0.695</td>
<td>0.270</td>
</tr>
<tr>
<td>L diaphragm</td>
<td>0.385</td>
<td>0.054</td>
</tr>
<tr>
<td>R diaphragm</td>
<td>0.690</td>
<td>0.323</td>
</tr>
<tr>
<td>Mesentery</td>
<td>0.534</td>
<td>0.191</td>
</tr>
<tr>
<td>Cul de sac</td>
<td>0.806</td>
<td>0.806</td>
</tr>
<tr>
<td>Bladder peritoneum</td>
<td>0.041</td>
<td>0.000</td>
</tr>
<tr>
<td>Pelvic or para-aortic lymph nodes</td>
<td>0.571</td>
<td>0.092</td>
</tr>
</tbody>
</table>

\( \kappa > 0.61 \) represents substantial inter-rater agreement.
Peritoneal Cancer Index

Regions | Lesion Size | Lesion Size Score
---|---|---
0 Central | | LS 0 No tumor seen
1 Right Upper | | LS 1 Tumor up to 0.5 cm
2 Epigastrium | | LS 2 Tumor up to 5.0 cm
3 Left Upper | | LS 3 Tumor > 5.0 cm or confluence
4 Left Flank | | 
5 Left Lower | | 
6 Pelvis | | 
7 Right Lower | | 
8 Right Flank | | 
9 Upper Jejunum | | 
10 Lower Jejunum | | 
11 Upper Ileum | | 
12 Lower Ileum | | 

PCI

Sugerbaker, 1996
Cytoreductive Surgery (CRS)

- Gall Bladder
- Spleen
- Liver
- Stomach
- Uterus
- Colon
- Rectum
- Diaphragm

- Peritoneal Resection
- HIPEC
- Anastomosis

UCI
HIPEC (Hyperthermic Intraperitoneal Chemoperfusion)
Cytoreductive Surgery—How do we do it?
Cytoreductive Surgery—How do we do it?

Fig. 1  Anterior peritoneectomy

Abdominal Wall

Abdominal Retractor

Anterior Peritoneum

Izquierdo et al, JOGS 2019
Cytoreductive Surgery—How do we do it?

Fig. 2 Completed left upper quadrant peritonectomy

Abdominal Retractor

Spleen

Left Hemidiaphragm with its peritoneum stripped

Izquierdo et al, JOGS 2019
Cytoreductive Surgery—How do we do it?

Fig. 3  a, b Completed right hemidiaphragmatic peritoneectomy

Izquierdo et al, JOGS 2019
Cytoreductive Surgery—How do we do it?

Fig. 4  a, b Pelvic peritoneectomy with visceral resection

Izquierdo et al, JOGS 2019
Cytoreductive Surgery—How do we do it?

**FIGURE 1**  A, Hyperthermic intraperitoneal chemotherapy administered with an open technique allows continued manipulation of the abdominal and pelvic contents to achieve uniform distribution of heat and chemotherapy. A vapor barrier above the chemotherapy solution is created by four smoke aspirators. **B,** The closed method for hyperthermic perioperative chemotherapy is preferred by some surgeons.

*Deraco et al, Cameron’s *Current Surgical Therapy*
CRS/HIPEC in CRC with PM

- At median follow-up of 21.6 months, CRS/HIPEC arm median OS was **22.3 vs. 12.6** months in the control arm.

- Complete cytoreduction: median OS of **48 months**, with **45%** alive at **5 years**

Verwaal et al, JCO 2003
Verwaal et al, ASO 2008
Overall survival (ITT)

Median Follow Up: 64 months [95% CI: 58.9-69.8]

<table>
<thead>
<tr>
<th></th>
<th>HIPEC</th>
<th>Non-HIPEC</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Survival (months) [95% CI]</td>
<td><strong>41.7</strong> [36.2-52.8]</td>
<td><strong>41.2</strong> [35.1-49.7]</td>
<td>0.995</td>
</tr>
<tr>
<td>1-year Survival</td>
<td>86.9%</td>
<td>88.3%</td>
<td></td>
</tr>
<tr>
<td>5-year Survival</td>
<td>39.4%</td>
<td>36.7%</td>
<td></td>
</tr>
</tbody>
</table>

HR=1.00: 95%CI [0.73 - 1.37] p=0.995

Quenet et al, JCO 2018, presentation at ASCO 2018 (supp.)
NCCN Colon Cancer Guidelines

Synchronous liver only and/or lung only metastases

- Resectable
  - See Treatment and Adjuvant Therapy (COL-5)

- Unresectable (potentially convertible or unconvertible)
  - See Treatment and Adjuvant Therapy (COL-6)
  - See Primary Treatment (COL-7)

Synchronous abdominal/peritoneal metastases

- See Principles of Imaging (COL-A)
- See Principles of Pathologic Review (COL-B 4 of 5)
- See Principles of Surgery (COL-C 2 of 3)
NCCN Colon Cancer Guidelines

Synchronous abdominal/peritoneal metastases\(^{aa}\)

- Obstructed or imminent obstruction
  - Colon resection\(^{g, l}\)
    - or Diverting ostomy
    - or Bypass of impending obstruction
    - or Stenting
    - See Systemic Therapy (COL-D)

- Nonobstructing
  - See Systemic Therapy (COL-D)

\(^{aa}\)Consider colon resection only if imminent risk of obstruction, significant bleeding, perforation, or other significant tumor-related symptoms.

\(^{g, l}\)Complete cytoreductive surgery and/or intraperitoneal chemotherapy can be considered in experienced centers for select patients with limited peritoneal metastases for whom R0 resection can be achieved.
NCCN Colon Cancer Guidelines—2024

The panel currently believes that complete cytoreductive surgery and/or intraperitoneal chemotherapy can be considered in experienced centers for selected patients with limited peritoneal metastases for whom R0 resection can be achieved. However, the significant morbidity and mortality associated with HIPEC, as well as the conflicting data on clinical efficacy, make this approach very controversial.

Determining Resectability
The consensus of the panel is that patients diagnosed with potentially resectable mCRC should undergo an upfront evaluation by a multidisciplinary team, including surgical consultation (i.e. with an experienced hepatic surgeon in cases involving liver metastases) to assess resectability status. The criteria for determining patient suitability for resection of metastatic disease are the likelihood of achieving complete resection of all evident disease with negative surgical margins and maintaining adequate liver reserve. When the remnant liver is insufficient in size based on cross-sectional imaging volumetrics, preoperative portal vein embolization of the involved liver can be done to expand the future liver remnant. It should be noted that size alone is rarely a contraindication to resection of a tumor. Resectability differs fundamentally from endpoints that focus more on palliative measures. Instead, the resectability endpoint is focused on the potential of surgery to cure the disease. Resection should not be undertaken unless complete removal of all known tumor is realistically possible (R0 resection), because incomplete resection or debulking (R1/R2 resection) has not been shown to be beneficial.

The role of PET/CT in determining resectability of patients with mCRC is discussed in Workup and Management of Synchronous Metastatic Disease, below.

Neoadjuvant Therapy and Conversion to Resectability
The majority of patients diagnosed with metastatic colorectal disease have unresectable disease. However, for those with liver-limited unresectable disease that, because of involvement of critical structures, cannot be resected unless regression is accomplished, neoadjuvant systemic therapy is being increasingly considered in highly selected cases in an attempt to downsize colorectal metastases and convert them to a resectable status. Patients presenting with large numbers of metastatic sites within the liver or lung are unlikely to achieve an R0 resection simply based on a favorable response to therapy, as the probability of complete eradication of a metastatic deposit by systemic therapy alone is low. These patients should be regarded as having unresectable disease not amenable to conversion therapy. In some highly selected cases, however, patients with disease that has had significant response to conversion therapy can be converted from unresectable to resectable disease status.

Any active metastatic systemic regimen can be used in an attempt to convert a patient’s unresectable disease status to a resectable disease status, because the goal is not specifically to eradicate micrometastatic disease, but rather to obtain the optimal size regression of the visible metastases. An important point to keep in mind is that irinotecan- and oxaliplatin-based chemotherapeutic regimens may cause liver steatohepatitis and sinusoidal liver injury, respectively. Studies have reported that chemotherapy-associated liver injury (including severe sinusoidal dilatation and steatohepatitis) is associated with morbidity and complications following hepatectomy for colorectal liver metastases. To limit the development of hepatotoxicity, it is
Insurance Barriers

- Medical necessity
- Non-covered charge or service
- Medically unlikely edits (MUE)
- Additional clinical documentation needed
- Missing claim information
- Bundled and duplicate claims
- Billing and coding

Private insurance vs. Government insurance

Ong et al, ASO 2022
The Chicago Consensus on Peritoneal Surface Malignancies: Management of Colorectal Metastases

Chicago Consensus Working Group

Collaborators

Colorectal Cancer with Metachronous Peritoneal Metastasis

1. Metachronous Colorectal Cancer Peritoneal Metastases
   - H&P
   - Restaging CT/CAP
   - Consider PET CT
   - Complete Colonoscopy if indicated
   - Pathology Review
   - Determine MSI, KIAA, BRAF Status if unknown
   - CEA
   - Tumor Board

2. Metachronous Peritoneal Metastases Only
   - Low-risk Disease
   - Consider Diagnostic Laparoscopy
   - Assess PCI, Obtain Biopsies as Needed
   - If incomplete CRS is achieved, consider standard treatment, best supportive care, or clinical trial.

3. High-risk Disease
   - Chemotherapy: 3-6 mo: FOLFOX or FOLFIRI +/- Bevacizumab or FOLFOXIRI
   - Restaging Imaging: Consider Laparoscopy
   - Progression
     - Standard Treatment/Best Supportive Care or Clinical Trial

4. Widespread or Unresectable Solid-Organ Metastases
   - Of poor functional status
   - Systemic Chemotherapy
   - Clinical Trial
   - Best Supportive Care

*Clinical pathology features:
- Low risk: Disease-free interval >1 yr, Younger Age, LN-, Low Grade, Low PCI
- High risk: Disease-free interval <1 yr, Older Age, LN+, High Grade, High PCI
- Consider PS DDS for Risk Stratification

*Refer to Principles of Surgery for Patients with Resectable Liver and/or Lung Metastases in the Context of Peritoneal Metastasis
The Peritoneal Surface Malignancy Consortium

Our goal is to provide multidisciplinary recommendations for the management of peritoneal surface malignancies across various disease sites. The management of peritoneal surface malignancies remains controversial and poorly represented in national guidelines. Recognizing the need for increased awareness and appropriate management of peritoneal surface disease, our guidelines are meticulously developed with contributions from an esteemed array of PSM experts. Our collaborators include surgical oncologists, medical oncologists, pathologists, radiologists, palliative care providers, and nurses.

If you are looking to get involved in the PSM Consortium, please contact Varun and David for further information.

- varun.bansal@yale.edu
- david.yu@yale.edu
“Liquid Biopsy”


Analysis of Plasma Cell-Free DNA by Ultradeep Sequencing in Patients With Stages I to III Colorectal Cancer

Thomas Reinert 1, Tenna Vesterman Henriksen 1, Emil Christensen 1, Shruti Sharma 2, Raheleh Salari 2, Himanshu Sethi 2, Michael Knudsen 1, Iver Nordentoft 3, Hsin-Ta Wu 2, Antony S Tin 2, Mads Heilskov Rasmussen 1, Søren Vang 1, Svetlana Shchegrova 2, Amanda Frydendahl Boll Johansen 1, Ramya Srinivasan 2, Zoe Assaf 2, Mustafa Balcioglu 2, Alexander Olson 2, Scott Dashner 2, Dina Hafez 2, Samantha Navarro 2, Shruti Goel 2, Matthew Rabinowitz 2, Paul Billings 2, Styrmir Sigurjonsson 2, Lars Dyrsjøt 1, Ryan Swenerton 2, Alexey Aleshin 2, Søren Laurberg 3, Anders Husted Madsen 4, Anne-Sofie Kannerup 5, Katrine Stribolt 6, Søren Palmelund Krag 7, Lene H Iversen 3, Kåre Gotschalck Sune sen 6, Cheng-Ho Jimmy Lin 2, Bernhard G Zimmermann 2, Claus Lindbjerg Andersen 1
Novel Liquid Biopsy Approaches

Multimodal epigenetic sequencing analysis (MESA) of cell-free DNA for non-invasive colorectal cancer detection

Yumei Li1,2,1, Jianfeng Xu3,1, Chaorong Chen1, Zhenhai Lu4,1, Desen Wan6, Diange Li7, Jason S. Li1, Allison J. Sorg1, Curt C. Roberts5, Shivanii Mahajan5, Maxime A. Gallant5, Itai Pinkovskiy5, Ya Cui1, David J. Taggart3 and Wei Li1,2,*
Molecular characterization of colorectal cancer related peritoneal metastatic disease

Novel In Vitro Model

An in vitro vascularized micro-tumor model of human colorectal cancer recapitulates in vivo responses to standard-of-care therapy

Stephanie J Hachey¹, Silva Movsesyan, Quy H Nguyen, Giselle Burton-Sojo, Ani Tankazyan, Jie Wu, Tuyen Hoang, Da Zhao, Shuxiong Wang, Michaela M Hatch, Elizabeth Celaya, Samantha Gomez, George T Chen, Ryan T Davis, Kevin Nee, Nicholas Pervolarakis, Devon A Lawson, Kai Kessenbrock, Abraham P Lee, John Lowengrub, Marian L Waterman, Christopher C W Hughes

Summary

- Colorectal cancer is one of the most common cancers in the United States

- Management of colorectal cancer that has spread in the abdomen continues to evolve

- We are continually working to change the paradigm
Thank You!
oeng@hs.uci.edu