**Conflict of Interest Disclosure**

I do not have any required OHSU conflicts of interest to disclose.

Travel and lodging for educational workshops from Neuwave, Angiodynamics, and DaVinci.

---

**Overview of My Job**

- **Monday** = Operate & inpatient care
- **Tuesday** = Operate & inpatient care
- **Wednesday** = Clinic & inpatient care
- **Thursday** = Clinical Research, GI Trials, & inpatient care
- **Friday** = Clinical Research & inpatient care

- But...tumor boards->learning every day
  - Liver TB = Tues 7-8am
  - Pancreas = Wed 7-8am
  - Sarcoma = Wed 12-1pm
  - GI = Thurs 7-8 am

- Director of the Hepatic Arterial Infusion Program
- Knight Clinical Research and Review Committee (CRRC)

---

**Clinical and Research Program**

- Hepatopancreatoibiliary (HPB) Surgical Oncologist
  - 60% metastatic liver cancers (CRLM)
  - 20% pancreatic cancer
  - 10% primary liver cancers and biliary cancers (HCC, ICC, ECC, Hilar, and Gallbladder)

- 40% "protected" for research ("Thu and Fri")
  - Colorectal Liver Metastases (CRLM)
  - Intrahepatic Cholangiocarcinoma (ICC)
  - Hepatic Arterial Infusion (HAI)
  - Development of phase 1b/2 Trials for HPB Oncology

---

**Outline**

- Definition of Unresectable
- Colorectal liver metastasis
- Role of hepatic arterial infusion (HAI)
- Intrahepatic cholangiocarcinoma
- Converting the Unresectable
  - HAI + Systemic Therapy
  - Integration of Immuno-oncologics
Hepatic Resection for Liver Cancers

Where do we stand in 2021?

- Liver resection is safe
  - <2% 90-day mortality\(^1\)
  - Surgeon volume is important
- Only 10-20% resectable at presentation
- Recurrence remains high
  - 60-70% by 5 years\(^2\)
- Future = integration of systemic and regional treatment with resection

\(^1\)Mako SC JHP 2011. \(^2\)Hydon S. P. J. 2013.

Determination of Resectability

Early Referral to HPB Surgical Oncology

- Liver masses—referral to an HPB surgical oncologist at the onset for treatment planning
- Resectability involves:
  - Intact portal venous & hepatic arterial inflow
  - Intact hepatic venous & biliary outflow
  - Adequate future liver remnant (FLR) and role of liver volumetrics (>35%)
  - Need for portal vein embolization (PVE) and potentially hepatic vein embolization if small FLR

Colorectal Cancer Liver Metastases (CRLM)

Essential Multi-disciplinary Collaboration

- Approximately 50% of patients with colorectal cancer will develop CRLM
  - Synchronous disease: 20-34%
- Untreated CRLM is associated with a median survival of 5-8 months
  - Resected CRLM: >50% 5yr survival
  - Unresectable disease in eventually 80-90% of patients

Feng Y. Oncology. 2014.

Colorectal Cancer Liver Metastases

Tailoring the Treatment to the Biology

Median OS (mo)

<table>
<thead>
<tr>
<th>Study</th>
<th>Results of Liver Resection for Colorectal Metastases</th>
</tr>
</thead>
</table>
| C022  | Study arm: surgery; survival: 19.1 mos; median: 19.1 mos; stage: III/IV; site: liver; tumor: colon; chemotherapy: FOLFOX or FOLFIRI; adjuvant: FOLFOX or FOLFIRI + bevacizumab; number: 166 |}

Figure adapted from Axel Grotzky, MD and Charles Blanke, MD

The Era of Personalized Medicine

“Tailoring treatment based on a patient’s unique clinical attributes including genetics, key biomarkers, environmental factors, and personal preferences.”

Slide adapted from Kevin Billings, MD

Personalized Therapy for CRLM

- Personalized Operative Approach
  - Operation/s tailored to number, location of lesions
  - Underlying liver function
  - Overall health of patient
  - Chemotherapy response and tolerance

- Personalized Medical and Radiation Therapy
  - Full cancer mutational profiling
    - RAS status (KRAS, NRAS, BRAF)
    - MSI and MMR status
    - Laterality of CRC primary: short-course vs. long-course XRT

Two-Stage Hepatectomy for Bilateral CRLM

- Multiple and bilateral CRLM is not a contraindication to hepatic resection
- Goal: achieve an adequate future liver remnant (>30%) of two contiguous liver segments with vascular inflow/outflow and biliary outflow.

- Paradigm change: focus on what is left behind and not what needs to be removed.

Wat’s Possible...

Patient Case #1

39 yo woman with KRAS wt, BRAF wt, MSI-stable rectosigmoid cancer and > 30 bilateral liver metastases in every segment (9/9) of her liver
Three Weeks Ago...

How did she get there?

- **Preop**
  - 10 cycles FOLFOX + bevacizumab (David Cosgrove and then transition to Lopez)

- **Operation** on 5/4/18 = partial clearance of segment 2 and 3, HAI pump, and resection of rectosigmoid primary (Mayo & Herzig)

- 5/30 to 10/3 = HAI floxuridine + dexamethasone 5 cycles plus SYS FOLFOX 6 cycles (Lopez)

- 10/17 to 2/6/2019 = FOLFIRI + panitumimab (Lopez and Mayo)

- **Operation** on 3/21/19 = clearance of seg 2 & 3 with resection and MWA (lesions with 95% necrosis) (Mayo)

- Right portal vein embolization (PVE) on 4/11 (Interventional Radiology)
  - 2 cycles of FOLFIRI during liver hypertrophy

- Final operation on 6/6/19 = Extended R hepatectomy + caudate (Mayo)

Neoplastic Growths in the Liver

"Small vessels... from large parent arteries in the vicinity, form bizarre disorderly patterns that supply tumors"

Hepatic Arterial Infusion (HAI)

What's old is new... again?

Historical Aspects of HAI Therapy

The New England Journal of Medicine

Volume 270

February 13, 1964

Number 7

Chemotherapy of Metastatic Liver Cancer by Prolonged Hepatic-Artery Infusion

Robert D. Sullivan, M.D.,† John W. Norcross, M.D.,† and Elton Watkins, Jr., M.D.,‡

- Technique involved ligation of all non-hepatic branches of catheterized vessels & confirmation of placement with fluorescein, sewn directly into proper hepatic artery
- Treatment: 5-fluoro-2-deoxyuridine (FUdR) for 21-40 days... then yanked!
Drugs Used in HAI Therapy—Flouxuridine

- Higher liver extraction of flouxuridine vs. 5-FU during intraarterial therapy\(^1\)
- 100-400x increase in drug concentration due to high rate of 1st pass hepatic extraction (95%)
- FUDR = alternative pathway

\(^1\)Ensminger W. Sono Gastroenterol. 1963.

HAI Pump: Operative Technique

- Dissection of all vessels and ligation of accessory or replaced vessels
- Placement of catheter in ligated GDA
  - "Rule of Allen"

Assessing Perfusion
Hepatic and Extrahepatic

- Perfuse all liver segments
  - Cross-perfusion
- No extrahepatic perfusion of pancreas or duodenum
  - Skeletonization and clearance
- HAI pump bolus injection
  - Methylene blue
  - Fluorescein + Wood's lamp

Conversion to Resection: Phase I
HAI Flouxuridine/Dexamethasone + Systemic Oxaliplatin/Irinotecan

- Conversion to resection in \(n = 49\)
  - 47% overall (\(n = 23\); \(R_0 = 19\))
  - 57% in chemo-naive patients
- Median time to resection from HAIP
  - 7 months (range, 4 to 30 months)
- Operative characteristics
  - Portal Vein Embolization (PVE) = 12 patients
  - Two-stage hepatectomy = 4 patients
  - Combined RFA + resection = 10 patients
- Median OS from start of HAI therapy
  - 50.8 months chemotherapy-naive
  - 35 months previously treated


Patient Selection

- Who?
  - The right patient—this treatment program isn’t for everyone
  - Importance of SW Screening and social support
- OHSU Knight Tenets
  - **No** BRAF mutants and no MSI-H or MMR-d
  - Primary has to be resected
  - No evidence of extrahepatic disease
    - RP adenopathy, lung nodules, etc.
  - Biology tested with at least 6 cycles of systemic

Active HAI Program in the United States in 2021
Expanding in last 3 years mainly in the Eastern US

VoronoI Tessellation of NCI-Designated Cancer Centers

- NCI-Designated Cancer Centers designated by the NCI; the description provided is that of each center, with emphasis on where services are located.
It Takes a Team!

Patient Case #2

37 yo man with obstructing rectal CA 13 cm from anal verge and multiple (8) bilateral liver metastases

Case: Synchronous Rectal Cancer and Bilateral CRLM

A Tailored Approach

- Severely malnourished
- OR for laparoscopic diverting transverse colostomy and port
- Liver operation = two-stage hepatectomy
- Genotyping
  - KRAS, BRAF & NRAS wildtype
  - Loss of nuclear staining for MLH-1 and PMS2 = Microsatellite instable high (MSI-H)

Case: Synchronous Rectal Cancer and Bilateral CRLM

A Tailored Approach

- KEYNOTE-177 Trial
  - Phase III Randomized
  - Study of Pembrolizumab (MK-3475) vs Standard Therapy in Participants With Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Stage IV Colorectal Carcinoma
  - Randomized to pembrolizumab
    - 7 Cycles: Side effects...itchy eyebrow
  - OR
    - Laparoscopic resection of minor disease in left liver
    - Laparoscopic LAR and ostomy reversal
  - Path: 100% complete pathologic response in liver and primary

Management of Bilateral Disease

Management of Complex Metastatic Colorectal Cancer

- Many advances in peri-operative combinatorial systemic and biologic therapies dependent upon thorough cancer genetic profiling at the outset
- Management of patients with bilateral CRLM and/or synchronous disease requires seamless integration of the medical and surgical oncology teams to deliver a personalized approach tailored to the patients biology
- Response to HAI therapy in 22-62% with conversion to resection 30-50% for patients with unresectable CRLM
**Intrahepatic Cholangiocarcinoma (ICC)**

*A Unique Primary Liver Cancer*

- **2nd most common 1st liver cancer in the US**
  - US: 8,000 cases/year; Oregon: 80 cases/year

- **Increasing incidence**
  - Association with NAFLD and obesity...

- **Importance of tumor profiling of liver biopsy**
  - IDH-1, FGFR, MMR-dMSI-h, TMB, etc

---

**Case #1**

*What’s Possible with HAI + Systemic Therapy and Staged Hepatectomy*

68 yo healthy man with no underlying liver disease who presented with fatigue and a large liver mass biopsy proven locally advanced ICC with multifocal disease with no FGFR or IDH1 mutations and MSS
Case #2

The Importance of Next Generation Sequencing

64 yo healthy man with no underlying liver disease who presented with a large liver mass with biopsy confirming locally advanced ICC invading IVC with tumor thrombus in left and middle hepatic veins

Summary

Surgical Management of Unresectable Liver Disease

- Consultation with a hepatobiliary surgical oncologist at outset for treatment planning
- Full understanding of therapeutic, operative, and clinical trial options
- Timing of operation, future liver remnant, margins, lymphadenectomy, and supporting recovery
- Working with a dedicated multi-disciplinary team in an experienced center
Thank You