

Adjunctive Hepatic Arterial Infusion Conversion from Unresectable to Resectable

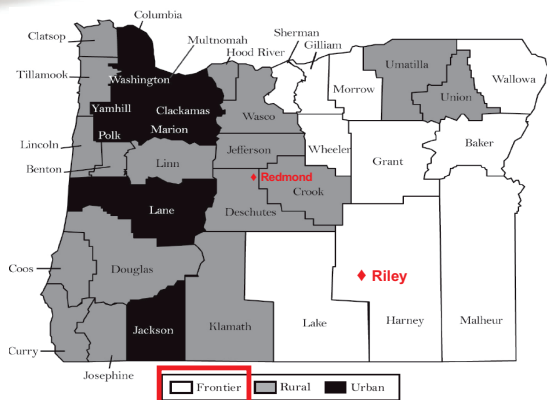
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Division of Surgical Oncology, Hepatopancreatobiliary Surgery
12 March 2021

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

Except...



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

- Hepatopancreatobiliary (HPB) Surgical Oncologist
 - 60% metastatic liver cancers (CRLM)
 - 20% pancreatic cancer
 - 10% RP sarcoma
 - 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

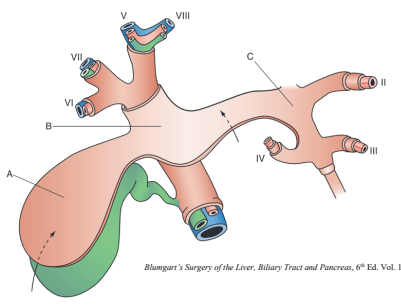


Outline

- Definition of Unresectable
- Colorectal liver metastasis
- Role of hepatic arterial infusion (HAI)
- Intrahepatic cholangiocarcinoma
- Converting the Unresectable
 - HAI + Systemic Therapy
 - Integration of Immuno-oncology



- Liver resection is safe
 - <2% 90-day mortality¹
 - Surgeon volume is important
- Only 10-20% resectable at presentation
- Recurrence remains high
 - 60-70% by 5 years²
- Future = integration of systemic and regional treatment with resection



Blumgart's Surgery of the Liver, Biliary Tract and Pancreas, 6th Ed. Vol. I.

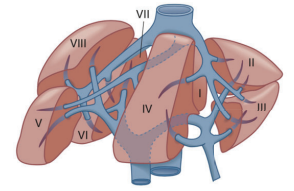
¹Mayo SC. *HPB*. 2011. ²Hyder O, Pawlik TM. *Surgery*. 2013.

- Liver masses—referral to an HPB surgical oncologist at the outset 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

Failure to Refer Patients with Colorectal Liver Metastases to a Multidisciplinary Oncology Team Should be a "Never-Event"

George Molina, M.D., M.P.H.
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 Cristina R. Ferrero, M.D.
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 Author affiliations: Division of Surgical Oncology, Department of Surgery, Massachusetts General Hospital, Boston, MA, USA; Harvard Medical School, Boston, MA, USA

Molina et al. *J National Med Assoc.* 2020.



Unresectable Colorectal Liver Metastases (CRLM)

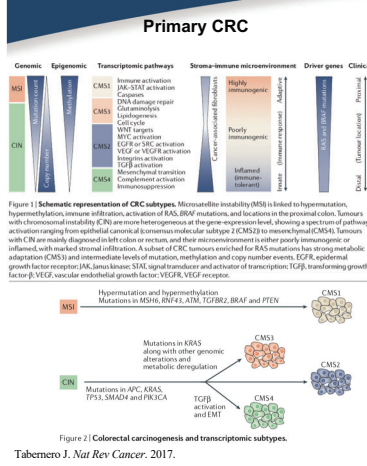
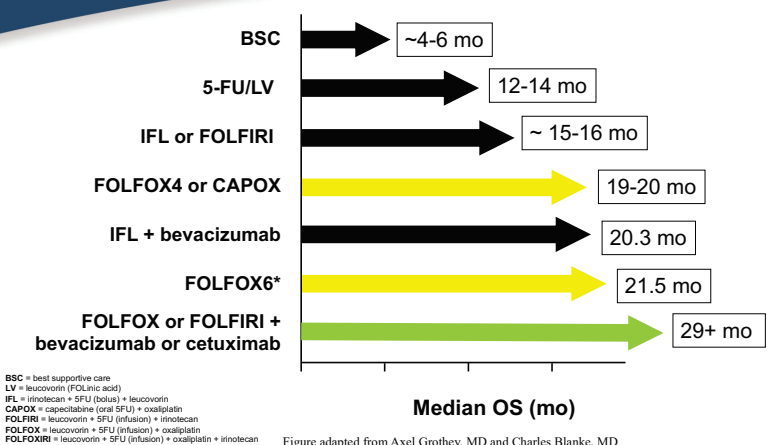
Essential Multi-disciplinary Collaboration

- 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

Study	N	Operative Mortality %	1-yr Survival %	3-yr Survival %	5-yr Survival %	10-yr Survival %	Median Survival (mo)
Gayowski 1994[10]	204	0	91	-	32	-	33
Scheele 1995[5]	434	4	85	45	33	20	40
Nordlinger 1996[6]	1568	2	80	-	28	-	40
Fong 1996[7]	1001	2.8	89	57	36	22	42
Minagawa 2000[11]	235	0.85	-	51	38	26	-
Adam 2001[4]	335	1	91	66	48	30	52
Choti 2002[12]	226	1	93	57	40	26	46
Kato 2003[13]	585	0	-	-	33	-	-
Figueras 2007[17]	501	4	88	67	42	36	44
Torlimson 2007[18]	612	-	-	-	-	17	44
Ress 2008[19]	929	1.5	-	-	36	23	43
House 2010[15]	563	1	-	69	51	37*	64
Nathani 2010[20]	949	0.9	-	65	45	22	52

* 5-yr survival.

Fong Y. *Oncology*. 2014.



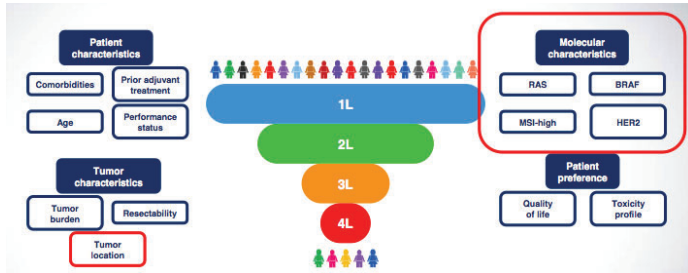
	Metastatic CRC		
	Subtype 1 canonical	Subtype 2 immune	Subtype 3 stromal
Frequency	33%	28%	39%
Molecular signatures	Immune and stroma E2F/MYC signaling DNA damage and cell cycle	Immune KRAS signaling p53 pathway	TGFβ KRAS signaling EMT and angiogenesis
Specific mutations	NOTCH1 and PIK3CB	NRAS, CDKN2, and EBF1	SMAD9
Metastatic recurrences	Many	Few	Many
Overall survival	Intermediate	Favorable	Unfavorable

Figure 3 | Stratified by SNF subtype. Piroda SP. *Nat Comm.* 2018.

Subtype	1	2	3
No. at risk	31	25	17
Subtype 1	31	25	17
Subtype 2	26	24	19
Subtype 3	36	28	15

The Era of Personalized Medicine

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

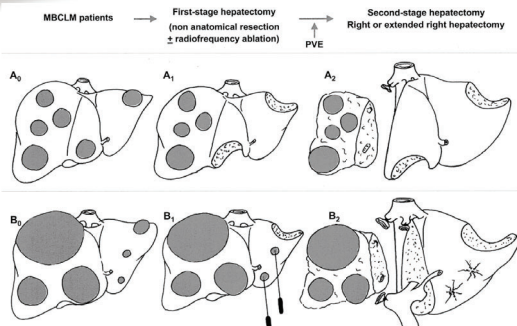


Slide adapted from Kevin Billingsley, MD

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.

Jaeck. *Ann Surg.* 2004;240: 1037–1051.

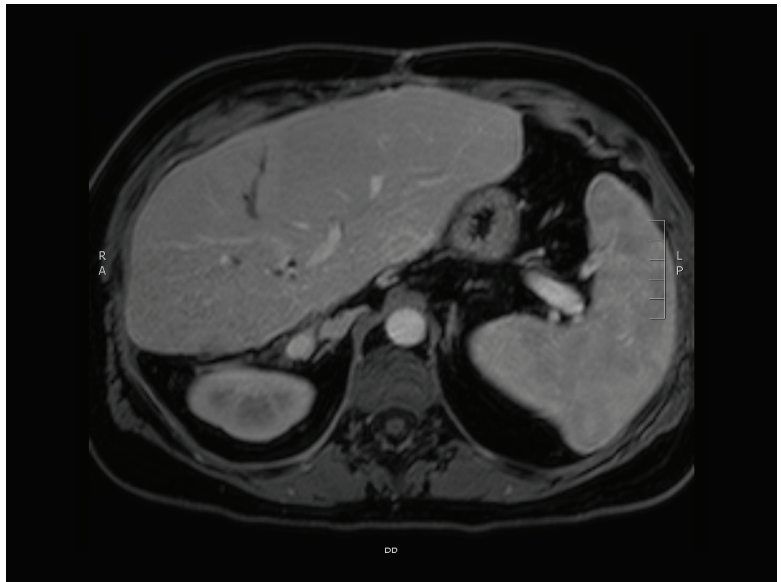
What's Possible...

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...

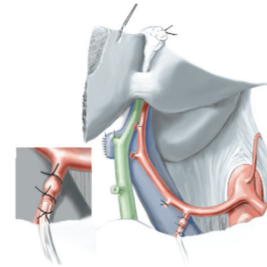


How did she get there?

- **Preop**
 - 10 cycles FOLFOX + bevacizumab (*David Cosegrove 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*)

Hepatic Arterial Infusion (HAI)

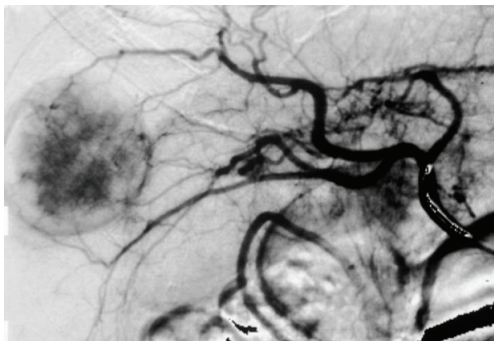
What's old is new...again?



Fong Y. *Atlas UGI & HPB Surgery*. Springer, 2007.

Neoplastic Growths in the Liver

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



Historical Aspects of HAI Therapy

The New England Journal of Medicine

Copyright, 1964, by the Massachusetts Medical Society

Volume 270

FEBRUARY 13, 1964

Number 7

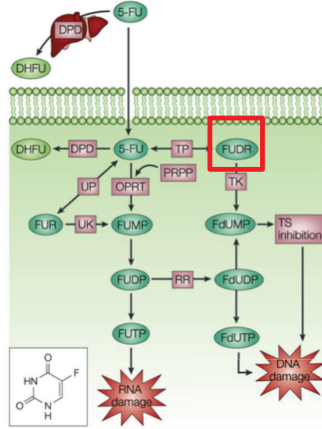
CHEMOTHERAPY OF METASTATIC LIVER CANCER BY PROLONGED HEPATIC-ARTERY INFUSION*

ROBERT D. SULLIVAN, M.D.,† JOHN W. NORCROSS, M.D.,† AND ELTON WATKINS, JR., M.D.‡
BOSTON, MASS.

- 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!

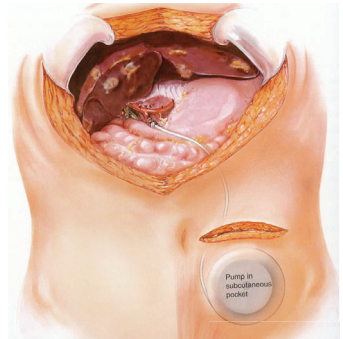
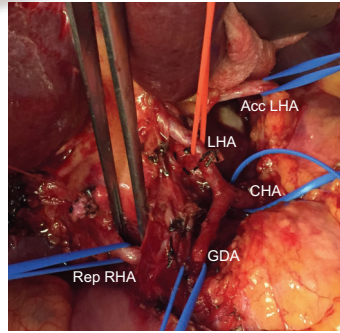
Drugs Used in HAI Therapy—Floxuridine

- Higher liver extraction of floxuridine vs. 5-FU during intra-arterial therapy¹
- 100-400x increase in drug concentration due to high rate of 1st pass hepatic extraction (95%)
- FUDR = alternative pathway



¹Ensminger W. *Semin Oncol*. 1983.
Longly DB. *Nature Reviews, Cancer*. 2003.

HAI Pump: Operative Technique

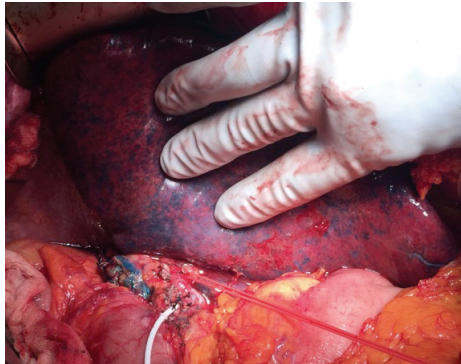


Cameron JL. *Atlas GI Surg*, 2nd Ed. Vol. 1.

- Dissection of all vessels and ligation of accessory or replaced vessels
- Placement of catheter in ligated GDA
 - "Rule of Allen" Allen PK. *J Am Coll Surg*. 2006: 57-65.

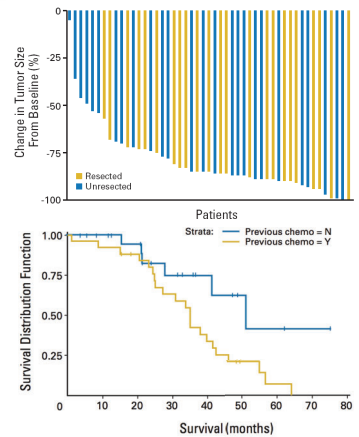
Assessing Perfusion Hepatic and Extrahepatic

- 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 Floxuridine/Dexamethasone + Systemic Oxaliplatin/Irinotecan

- Conversion to resection in n = 49
 - 47% overall (n = 23; R0 = 19)
 - 57% in chemo-naïve patients
- Median time to resection from HAIP
 - 7 months (range, 4 to 32 months)
- Operative characteristics
 - Portal Vein Embo (PVE) = 12 patients
 - Two-stage hepatectomy = 4 patients
 - Combined RFA+ resection = 10 patients
- Median OS from start of HAI therapy
 - 50.8 months chemotherapy-naïve
 - 35 months previously treated

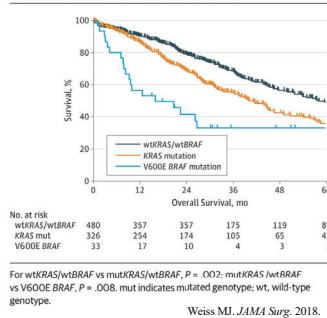


Kemeny NE. *J Clin Oncol*. 2009; 27(21): 3465-3471.

Patient Selection

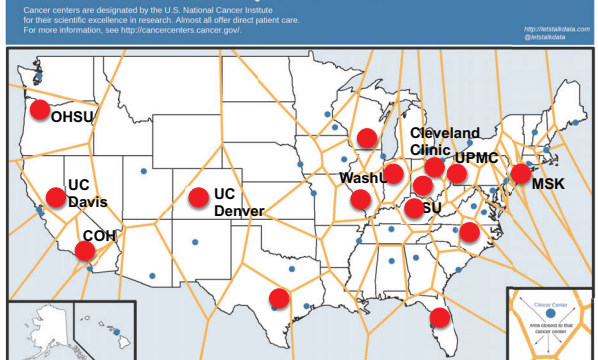
- Who?
 - The right patient—this treatment program isn't for everyone
 - Importance of SW Screening and social support
- OHSU Knight Tenets
 - **No** BRAF mutants and no MSI-H or MMR-d
 - Primary has to be resected
 - No evidence of extrahepatic disease
 - RP adenopathy, lung nodules, etc.
 - Biology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

Figure 2. Kaplan-Meier Estimates of Overall Survival

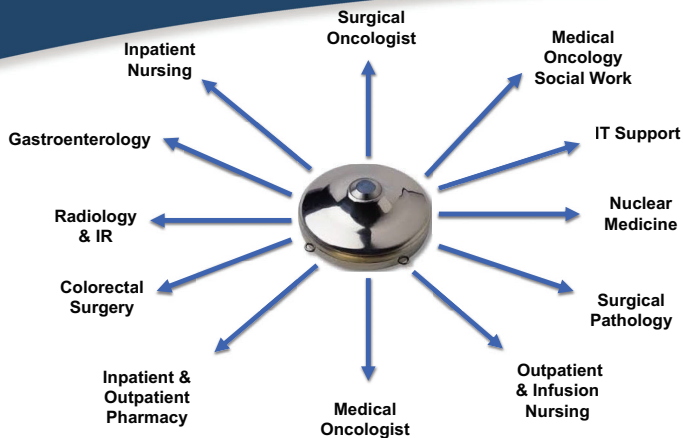


Active HAI Program in the United States in 2021 Expanding in last 3 years mainly in the Eastern US

Voronoi Tessellation of NCI-Designated Cancer Centers



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

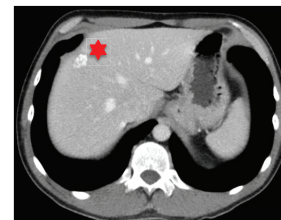
Case: Synchronous Rectal Cancer and Bilateral CRLM A Tailored Approach

- 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)



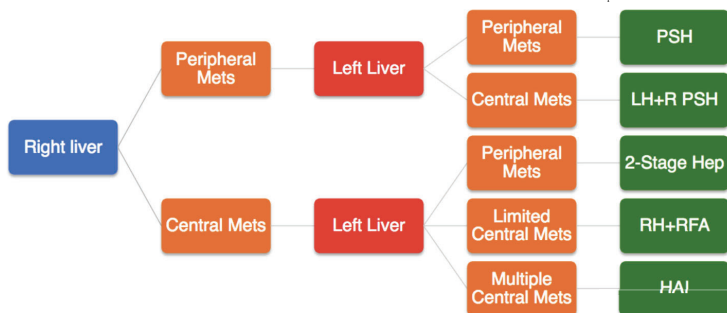
Case: Synchronous Rectal Cancer and Bilateral CRLM A Tailored Approach

- 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

PSH – Parsymal Sparing Hepatectomy
 LH – Left Hepatectomy
 R PSH – Right PSH
 RH – Right Hepatectomy
 RFA – Radiofrequency Ablation (Microwave)
 HAI – Hepatic Arterial Infusion



Summary

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

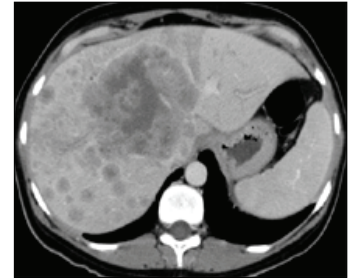
Intrahepatic Cholangiocarcinoma (ICC)

A Unique Primary Liver Cancer

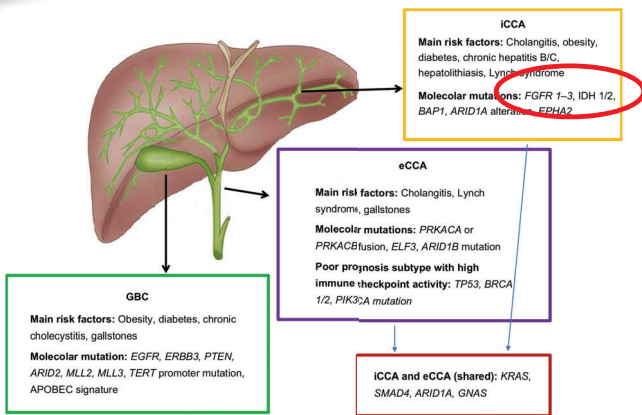
Intrahepatic Cholangiocarcinoma (ICC)

Large often multifocal liver disease

- 2nd most common 1^o 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-d/MSI-h, TMB, etc



The Changing Landscape of ABCs

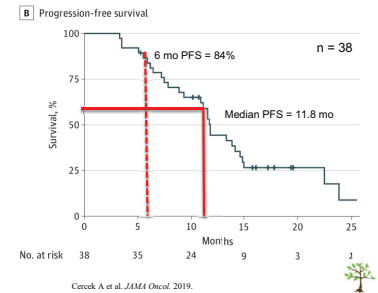


JAMA Oncology | Original Investigation

Assessment of Hepatic Arterial Infusion of Floxuridine in Combination With Systemic Gemcitabine and Oxaliplatin in Patients With Unresectable Intrahepatic Cholangiocarcinoma A Phase 2 Clinical Trial

Andrea Cercok, MD; Thomas Boerner, MD; Benjamin R. Tan, MD; Joanne F. Chou, MPH; Mithat Gönen, PhD; Taryn M. Boucher, BA; Haley F. Hauser, BA; Richard K. G. Do, MD; Maeve A. Lowery, MD; James J. Harding, MD; Anna M. Varghese, MD; Diane Reidy-Lagunes, MD; Leonard Saltz, MD; Nikolaus Schultz, PhD; T. Peter Kingham, MD; Michael I. D'Angelica, MD; Ronald P. DeMatteo, MD; Jeffrey A. Drebin, MD; Peter J. Allen, MD; Vinod P. Balachandran, MD; Kian-Huat Lim, MD; Francisco Sanchez-Vega, PhD; Neeta Vachharajani, BS; Maria B. Majella Doyle, MD; Ryan C. Fields, MD; William G. Hawkins, MD; Steven M. Strasberg, MD; William C. Chapman, MD; Luis A. Diaz Jr, MD; Nancy E. Kemeny, MD; William R. Jarnagin, MD

- n = 42 patients enrolled in 2 centers, n=38 received HAI + SYS
- 92% chemo-naïve
- Grade 4 adverse events in 11% requiring removal from study
- 4 patients (11%) converted to resection; 1 with complete pathologic response
- Median OS = 25 mo; 1 yr OS = 90%



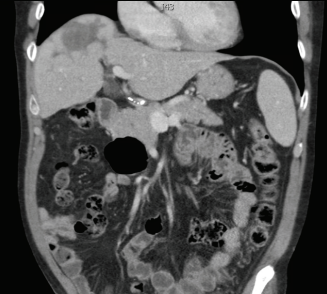
Case #1

What's Possible with HAI + Systemic Therapy and Staged Hepatectomy

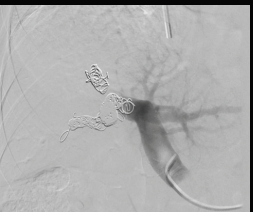
68 yo healthy man with no underlying liver disease who presented with fatigue and a large liver mass biopsy proven locally advanced ICC with multifocal disease with no FGFR or IDH1 mutations and MSS

Baseline

After 12 months HAI + SYS



Integration of HAI for Conversion to Resection



Final Pathologic Diagnosis

A. Liver, extended right hepatectomy:

- Focal residual adenocarcinoma within extensive fibrosis (see comment)
- Extensive embolic material with foreign body giant cell reaction

B. Liver, segment 3, wedge resection:


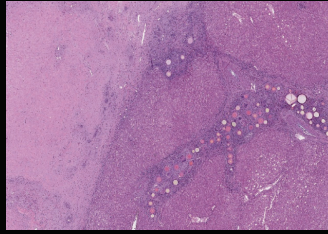
- Negative for tumor
- Embolic material with associated changes

C. Lymph node, portal nodes lymphadenectomy:

- Three lymph nodes negative for metastasis (0/3)

D. Abdominal, bile duct margin:

- Negative for tumor

Integration of HAI for Conversion to Resection

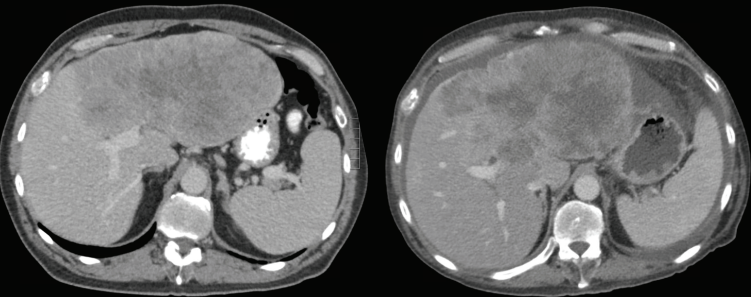
Case #2

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

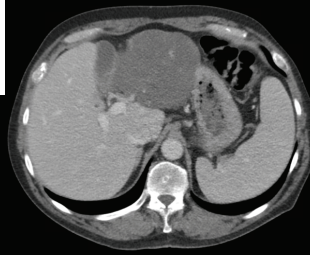
Integration of HAI for Conversion to Resection

Baseline **After 8 cycles FOLFIRINOX**



Integration of HAI for Conversion to Resection

12 cycles Pembrolizumab



GENERAL'S COMPREHENSIVE SOLID TUMOR PANEL: 19KD-304P0005
 Order: 22081108
 Collected: 5/25/2019 12:00 Status: Final result. Visible to patient: No (Not Released) Dx: Cholangiocarcinoma (HCC)

Component: GENERAL'S COMPREHENSIVE SOLID Tumor Panel Positive

TUMOR PANEL: Positive

SAMPLE TESTED: Liver mass, ultrasound guided core needle biopsy

DIAGNOSIS REPORTED: Adenocarcinoma

MICROSATELLITE INSTABILITY STATUS: Positive (MSI-High)

ESTIMATED TUMOR MUTATION BURDEN (TMB): 90 mutations/Mb (High)

Alterations of Strong Clinical Significance (Tier 1)

KRAS p.G12V and p.G77D. The G12V mutation is known to activate KRAS signaling and confers resistance to EGFR-targeted therapies. The G77D mutation has not been characterized.

MLH1 p.R473H and p.A165S. While the A165S variant has not been characterized, the R473H mutation is predicted to be pathogenic and, based on its allelic fraction, is a likely culprit for the microsatellite instability in this tumor. Whether the mutation is germline cannot be determined from tumor DNA, but given the patient's family history of cancer consideration might be given to refer for genetic counseling.

Final Pathologic Diagnosis

A. Peritoneal fat, excision:

- Fibrovascular adipose tissue.
- Negative for malignancy.

B. Gallbladder, cholecystectomy:

- Gallbladder with no diagnostic abnormality.

C. Portal lymphadenectomy:

- Three lymph nodes, negative for malignancy (0/3).

D. Liver, extended left hepatectomy:

- Liver with necrosis and fibrosis, consistent with complete treatment response (see comment).
- Negative for residual carcinoma.

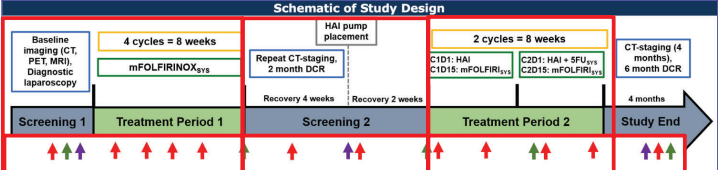
Comment: The tumor bed is extensively sampled, in 13 tissue blocks. Microscopic examination shows tumor bed with abundant necrosis, fibrosis, mucoid change, calcification, and chronic inflammation. No residual viable carcinoma is identified. The findings are consistent with complete treatment response. The background hepatic parenchyma contains ~5% macrovesicular steatosis.

Integration of HAI for Conversion to Resection

OHSU Phase II Unresectable ICC HAI Trial

<https://clinicaltrials.gov/ct2/show/NCT04251715>

Schematic of Study Design



Primary Objectives

- Efficacy of systemic mFOLFIRINOX followed by HAI fluoridine-DEX with systemic mFOLFIRI, DCR @ 6 months
- Safety of HAI fluoridine-DEX delivered concurrently with systemic mFOLFIRI

Secondary Objectives

- Overall Response Rate
- 1-year Overall Survival (OS)
- 1-year Progression Free Survival
- Post-operative complications (Clavien-Dindo Grade ≥ 3)

Exploratory Objectives

- Characterize tumor derived circulating hybrid cells (Wong)
- Evaluate Quality of Life (QoL) (Hansen)
- Examine microRNA expression patterns (Anand)
- Evaluate Radiographic Response using DW-MRI (Fung)
- Effect on immune microenvironment (Eli)
- Examine changes in HuR survival network (Brody)
- Characterize exceptional responders & non-responders (Corless)

Trial Status

- IRB & Cancer Institute Approved (#16033)
- NCT04251715
- Trial open for accrual: November 1, 2020
- Investigator-initiated trial funded by the OHSU Knight Cancer Institute

OHSU Knight Contact

PI: Skye C. Mayo, MD, MPH
 Division of Surgical Oncology
 503-494-5501

Knight Cancer Institute, Clinical Trials
trials@ohsu.edu, 503-494-1080

Integration of HAI for Conversion to Resection

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

