Colorectal Liver Metastases

Hepatic Artery Infusion Pump *Revisited*

James C Padussis, M.D.
Associate Professor of Surgery
Division of Surgical Oncology

Illustrative Case

- ***44 yo male presents with blood in his stool and lower abdominal pain***
- ***Colonoscopy shows 5.5 cm near obstructing sigmoid colon mass***
- ***Biopsy shows adenocarcinoma, MMR proficient***
- ***MRI shows…***


120 mm
Lossy


120 mm
Lossy


120 mm
Lossy

Unresectable Liver Metastases

Systemic Chemotherapy

- FOLFOX
- FOLFIRI
- FOLFOXIRI

+/- Bevacizumab

- Cetuximab (KRAS WT, Left Sided)
- Immunotherapy (MSI-H)
- Encorafinib/Cetuximab/Binimetinib (BRAF V600E)

- Regorafenib
- Trifluridine/Tipiracil

Survival Data

Unresectable Liver Metastases

- 24 month median overall survival
- 10-15% 5-year survival

Third Line (Dismal Response Rates)

- Regorafenib – 6.4 months OS vs 5.0 months OS (CORRECT Trial)

- Trifluridine/Tipiracil – 7.1 months OS vs 5.3 months OS (RECOURSE Trial)

Cancer. 2022 Nov; 14(22): 5513.

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CAN WE DO BETTER!

Liver Directed Regional Therapies

Hepatic Tumors Failed to Stain when India Ink was injected into the portal vein, whereas Hepatic Tissue between the tumors became intensely black.

Metastases in the liver are perfused almost exclusively via the hepatic artery and normal hepatocytes derive most of their blood supply from the portal vein.

Charles Breedis, MD
Pathology
University of Pennsylvania
1954

FUDR

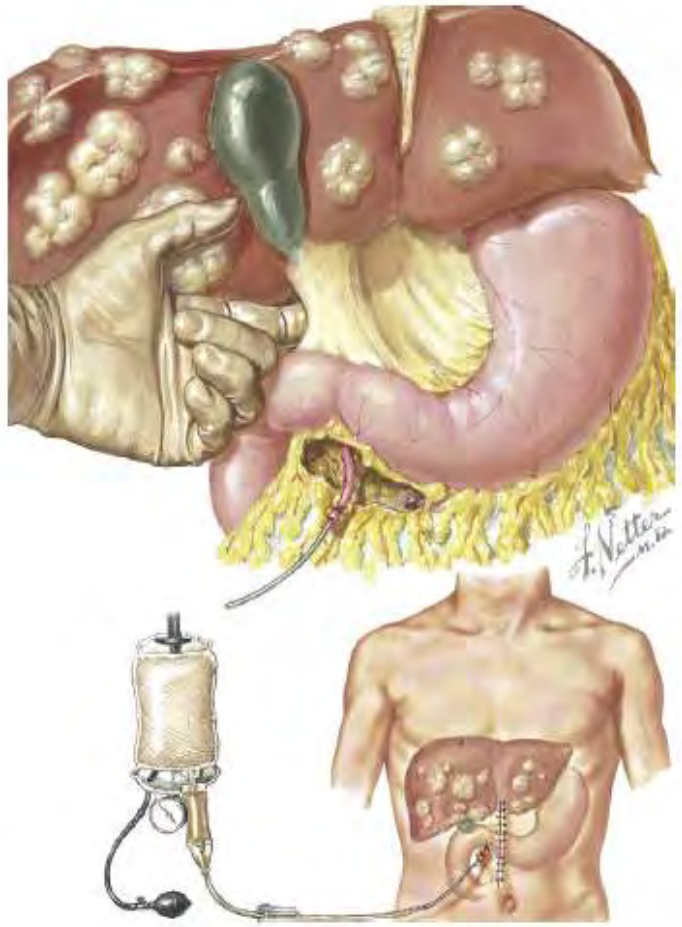
- Antimetabolite in which 94% is removed during the first pass in the hepatic arterial circulation.

"Nearly a one-pass Phenomenon."

- This allowed much higher doses of effective chemotherapy directly to the liver without systemic toxicity

1961 Miller and Griman Memorial Hospital

- Cannulated the GDA in retrograde fashion with a ureteral catheter that is brought out through the abdominal wall via a gastroepiploic stump
- Avoidance of extrahepatic infusion by ligating nearby arteries
- High rates of thrombosis, displacement, bleeding and air embolism
- Poor patient satisfaction



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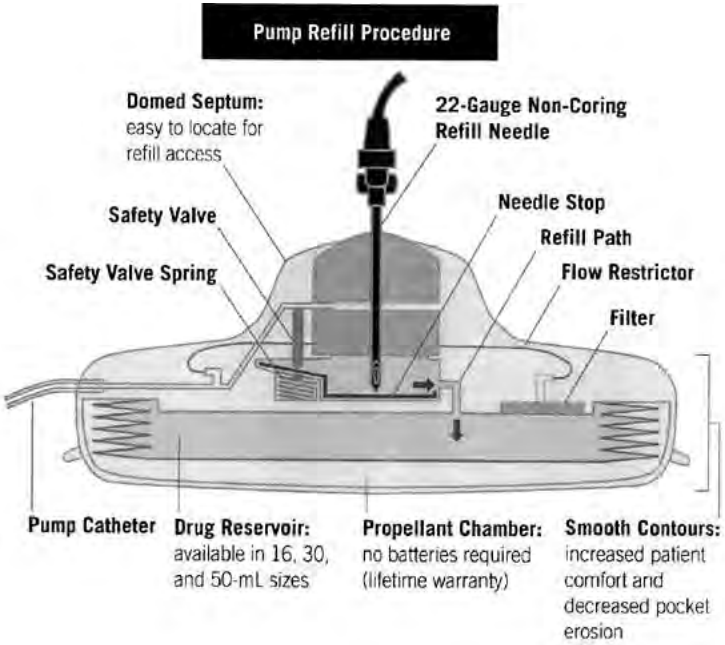
1970 Implantable Pump

Self contained, “inexhaustible” power source, using vapor pressure as the power source.



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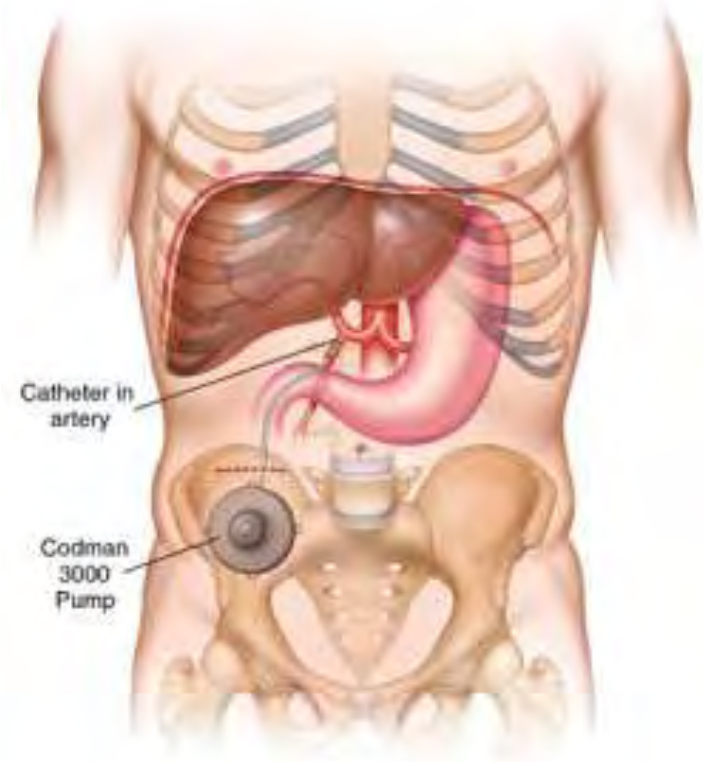
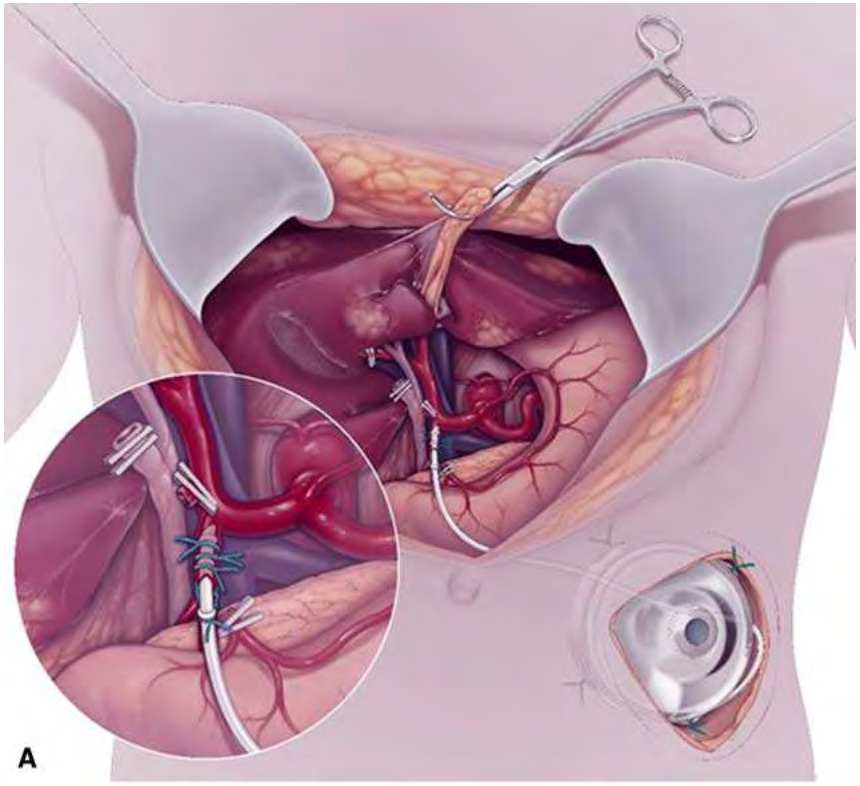
1980 Hepatic Arterial Infusion Pump

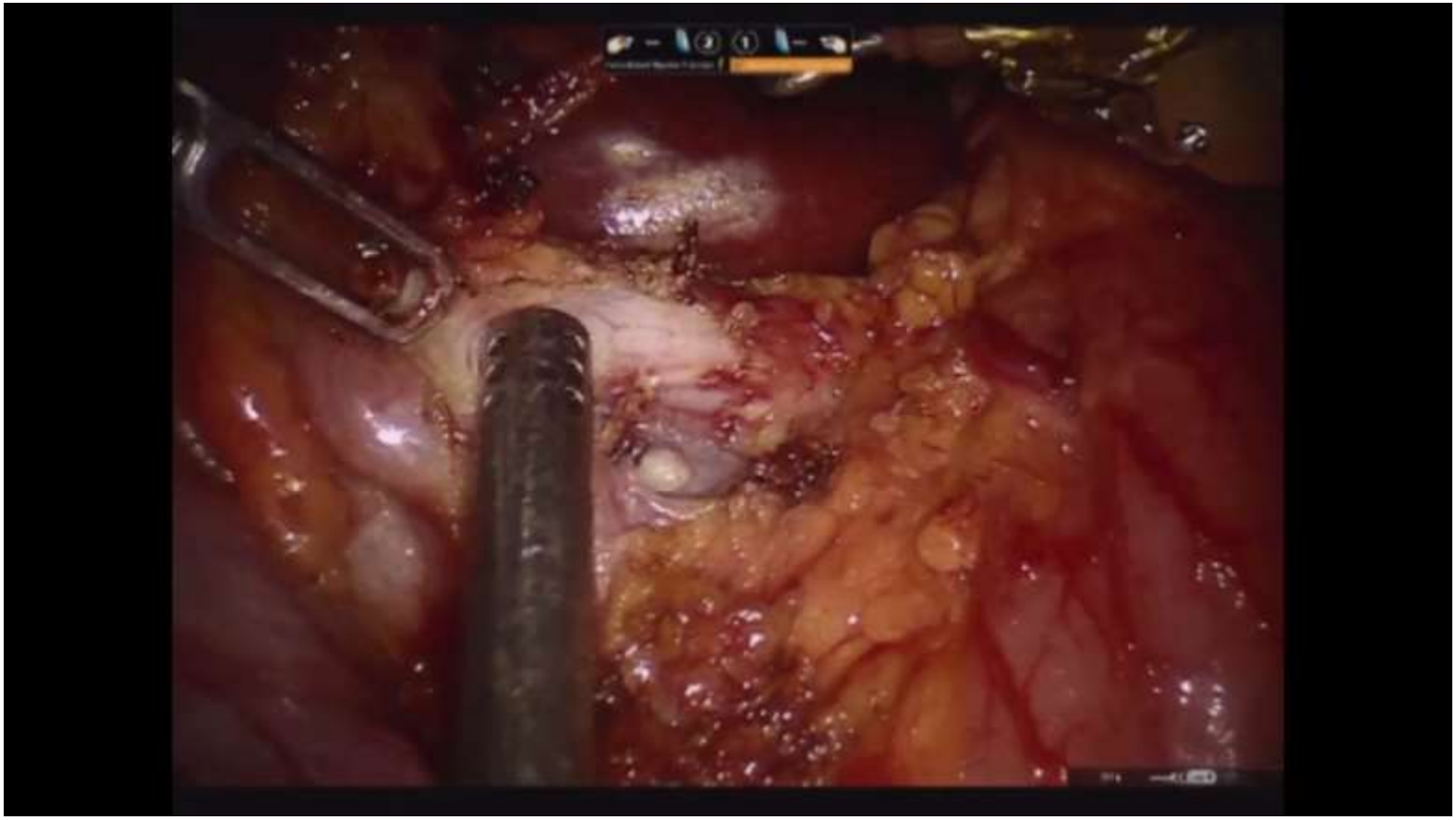
- Henry Buchwald published on first HAI-pump
- Intra-arterial FUDR is given via implantation of an infusion pump
- Allows for higher concentrations in the tumor mass and relative sparing of the normal liver



Operative Technique

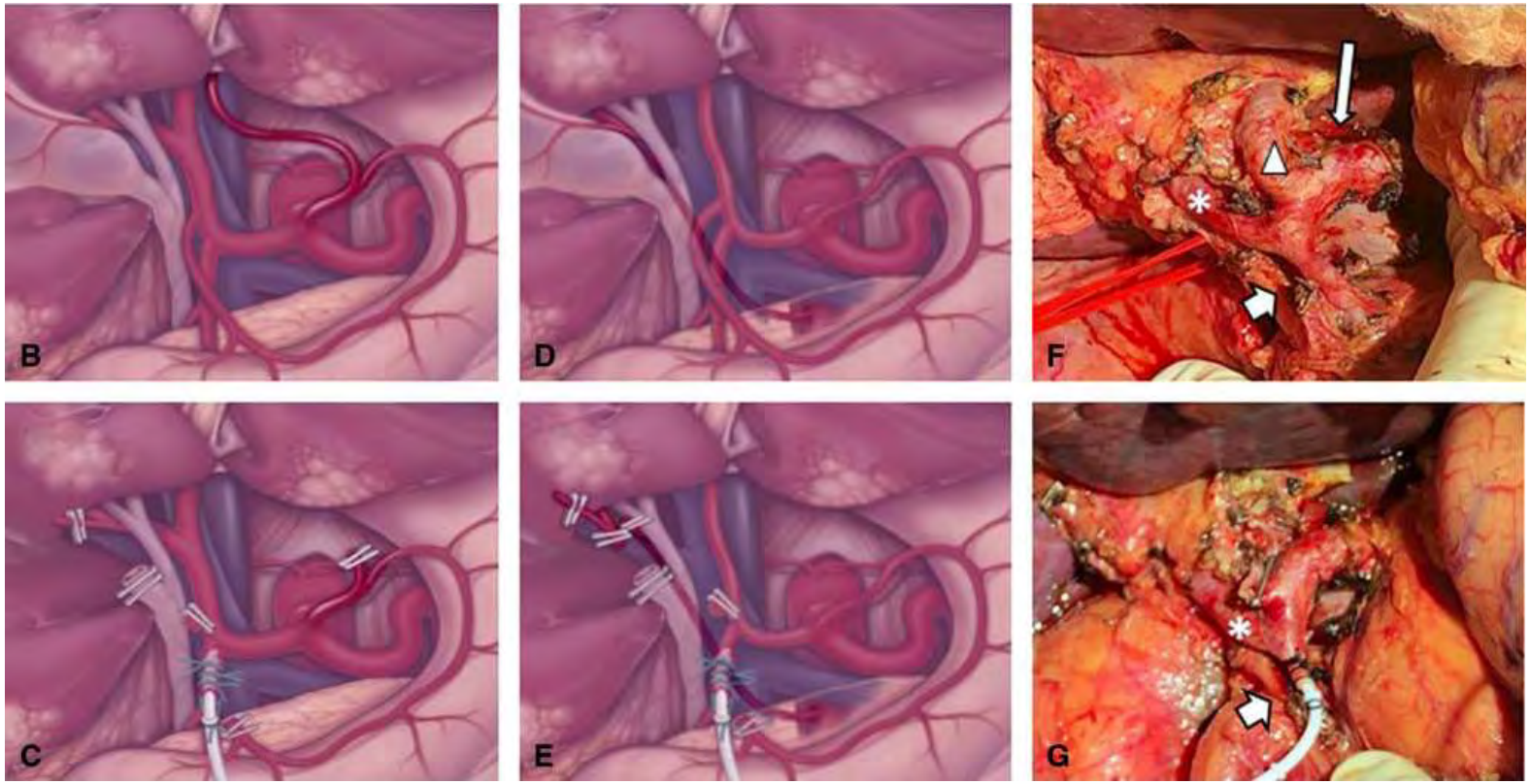
- Ex lap, ligate falciform ligament
- Ligate and Divide Right Gastric Artery
- Resect hepatic artery lymph node
- Isolate GDA and clear soft tissue around CHA and PHA
- Ligate GDA Branches
- Cholecystectomy
- Papaverine to GDA
- Cannulate and secure tubing
- Transverse SC pocket for pump
- Confirm no extrahepatic perfusion





Technical Considerations

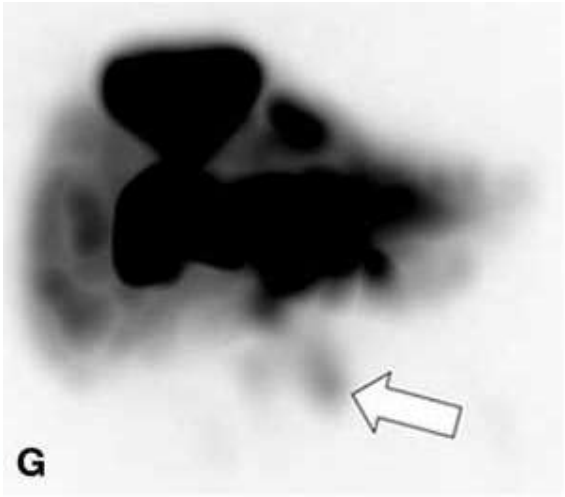
- Aberrant Anatomy



Sharib et al *Ann Surg 2022*

Technical Considerations

- Extrahepatic Perfusion



Sharib et al *Ann Surg 2022*

Technical Considerations

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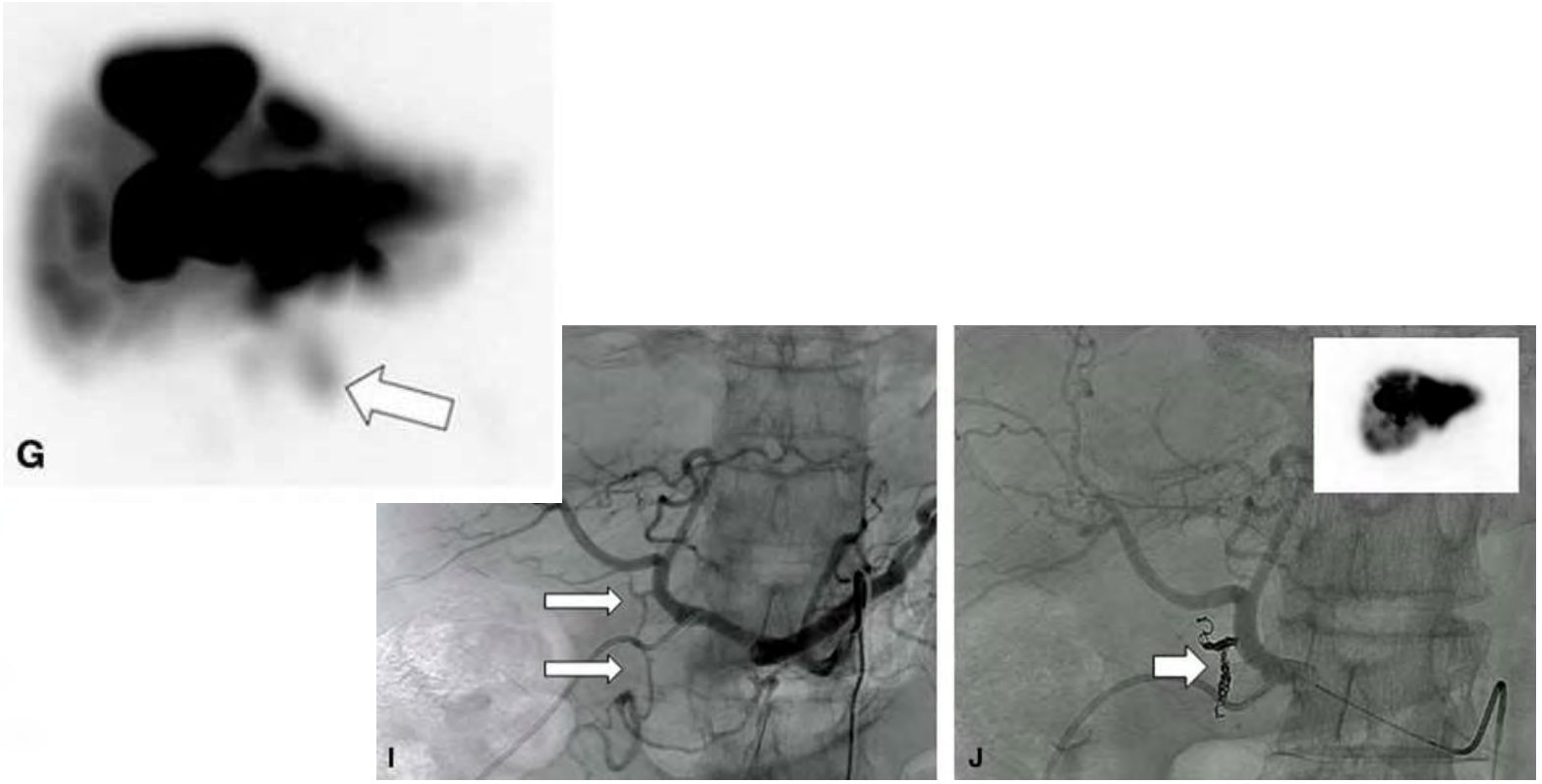


Sharib et al *Ann Surg 2022*

Morbidity

Overall 22%-28%

Peptic Ulcer (5-10%)
Extrahepatic Perfusion (6%)
Catheter Thrombosis (9%)
Pump Malfunction (6%)
SC Pocket Infection (6%)
Biliary Sclerosis (1-2%)

Patients can be rescued with prompt identification and aggressive intervention

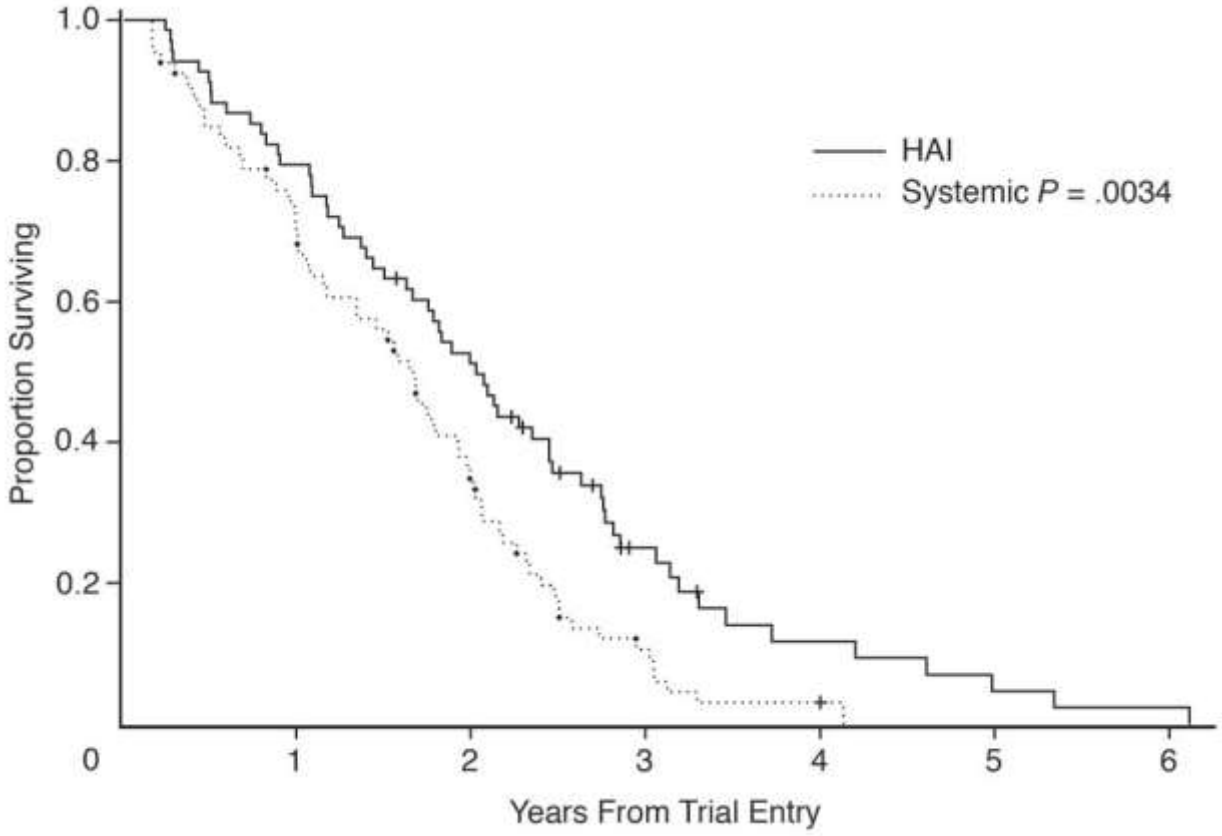
Chouliaras et al *HPB 2020*

Hepatic Arterial Infusion Versus Systemic Therapy for Hepatic Metastases From Colorectal Cancer: A Randomized Trial of Efficacy, Quality of Life, and Molecular Markers (CALGB 9481)

Kemeny et al *J Clin Oncol 2006*

- 135 patients with hepatic only, unresectable disease were randomly assigned HAI pump vs. systemic treatment (5FU/LV)
- Multicenter Trial (Jan 1996 – Dec 2000)
- Patients who previously received prior chemotherapy for metastatic disease were excluded
- No portal vein occlusion

CALGB 9481



OS Higher In HAI Group
24.4 mo vs 20.0 mo (p=0.0034)

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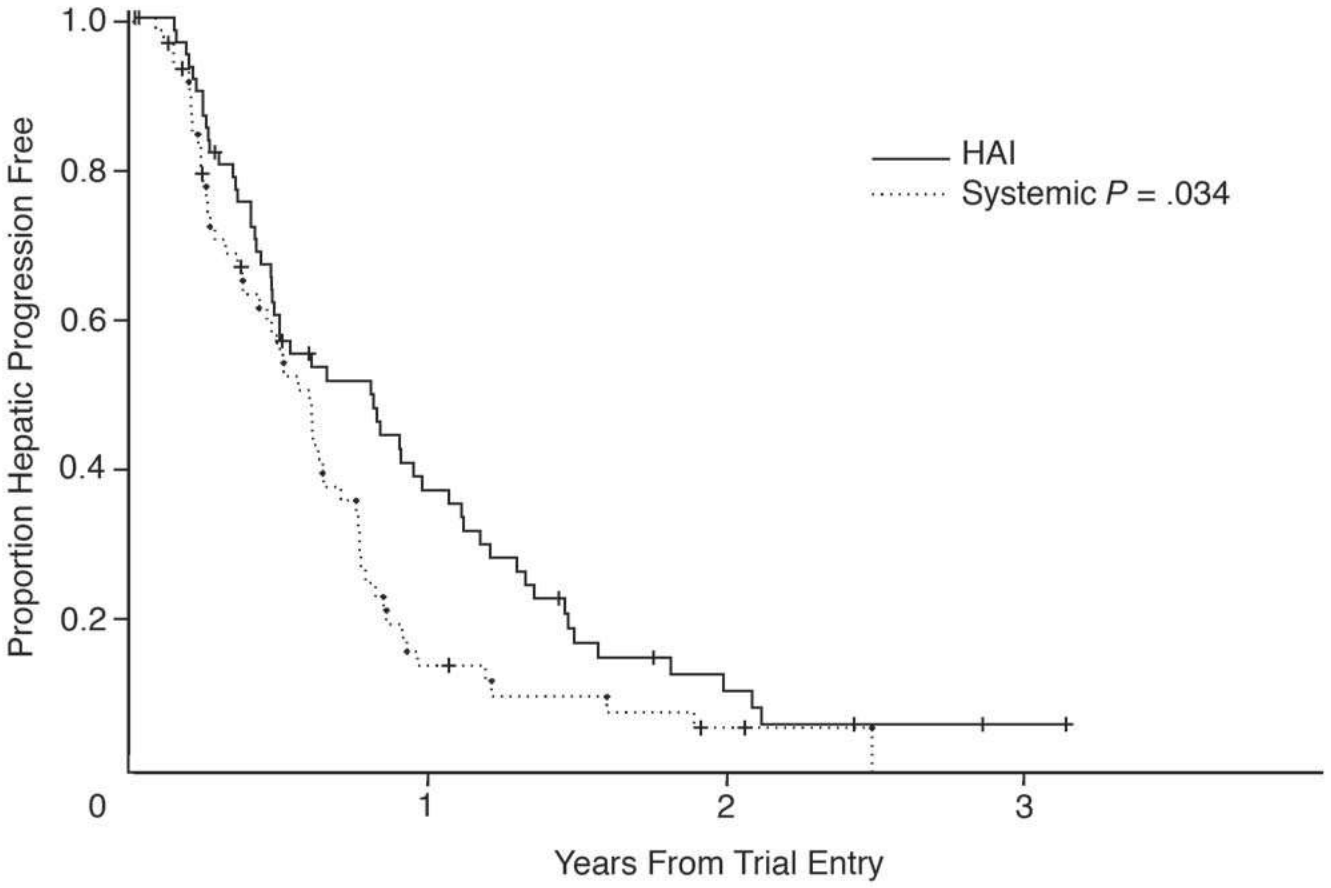
CALGB 9481



Hepatic PFS Higher In HAI Group (p=0.034)

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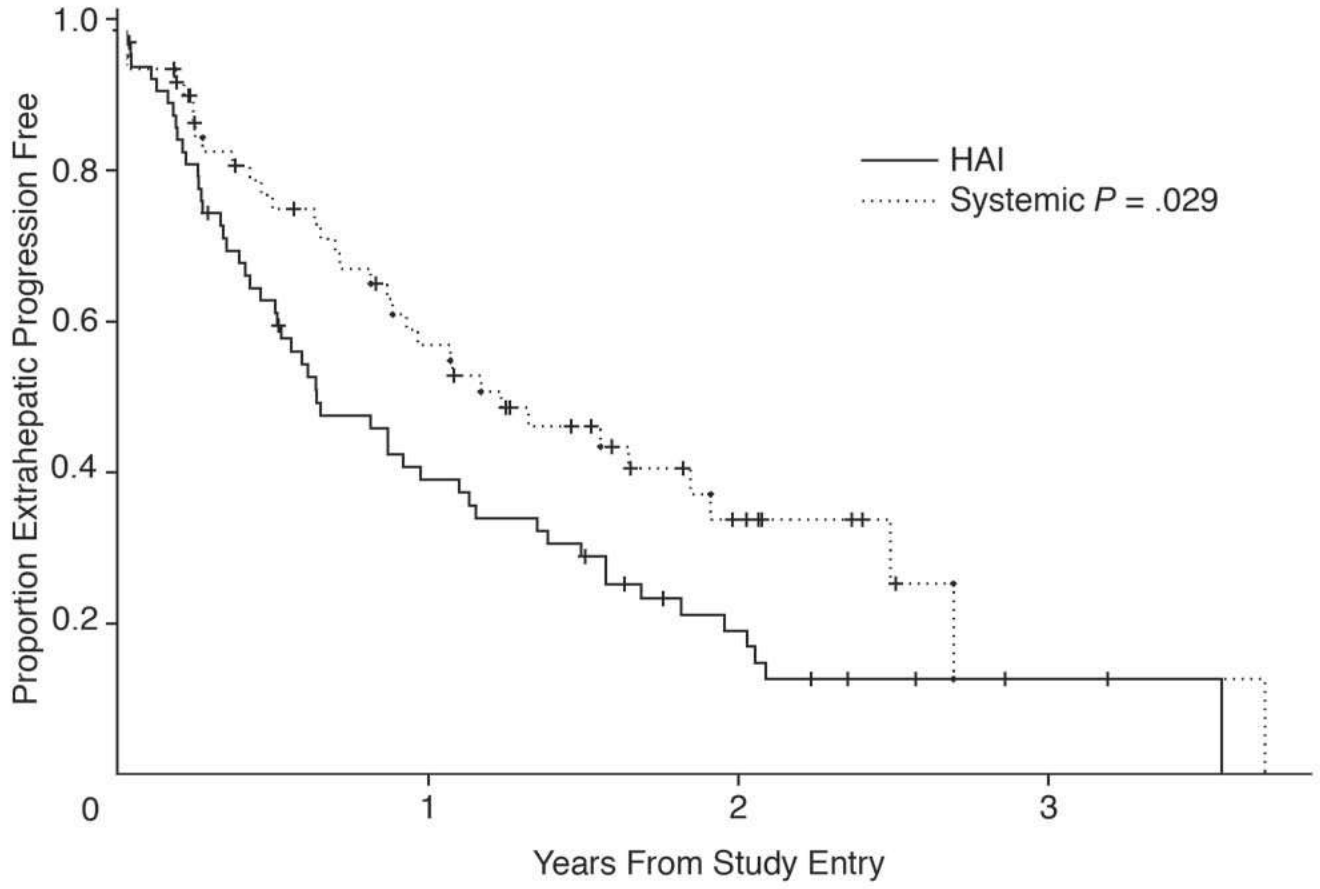

Extrahepatic PFS Higher In Chemo Group (p=0.034)

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CALGB 9481

Critiques:

- Did not compare modern chemotherapy (bolus 5-FU)
- Pump therapy given without systemic treatment
- >90% of HAI pumps placed at MSK

Questions:

- Can pump therapy work outside of a high-volume single institution?
- How does pump therapy compare to modern chemotherapy?
- Can systemic chemotherapy be given with HAI-pump?

Conversion to Resection

Phase II trial of hepatic artery infusional and systemic chemotherapy for patients with unresectable hepatic metastases from colorectal cancer: Conversion to resection and long-term outcomes

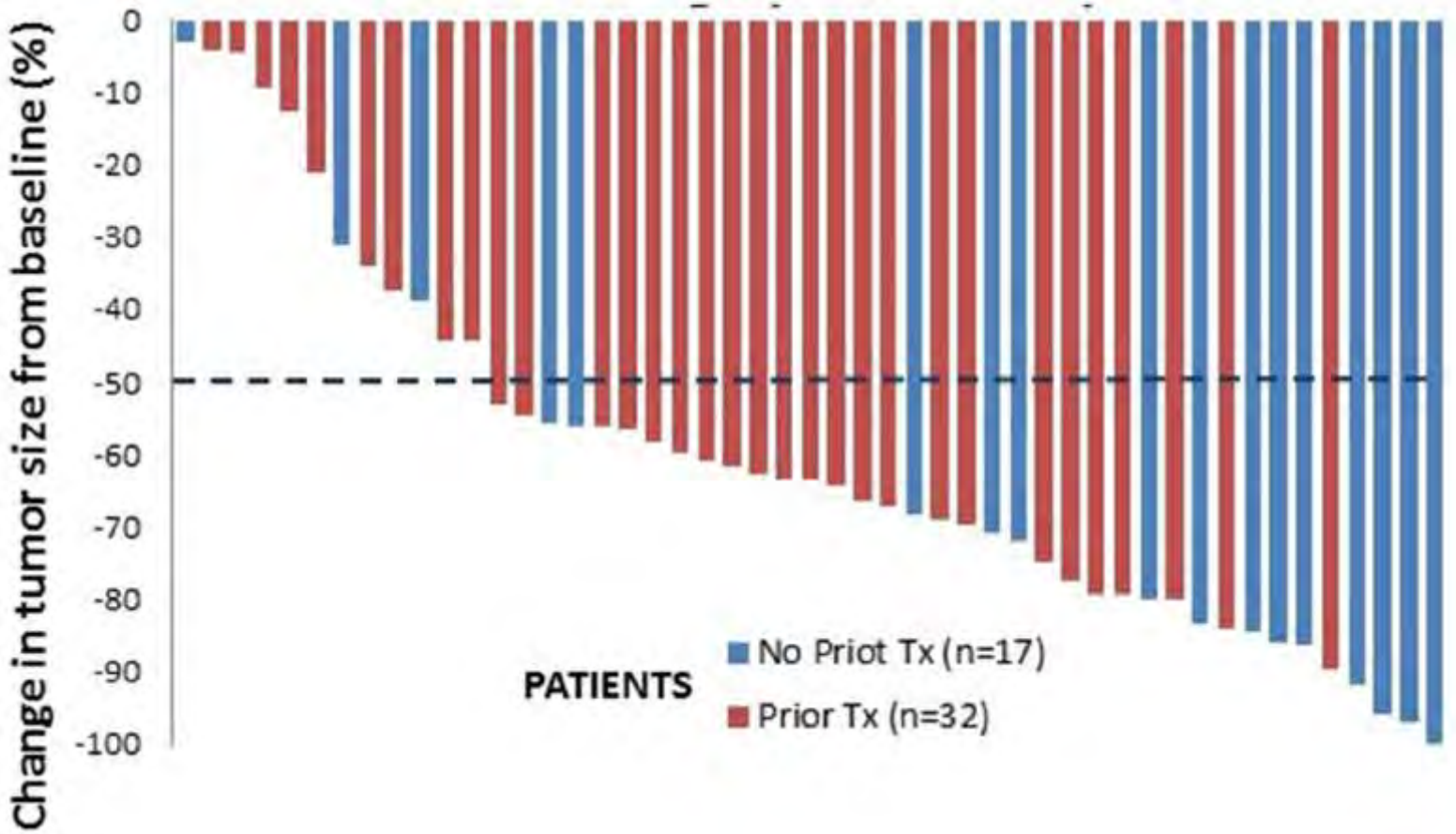
D'Angelica et al *Ann Surg 2015*

Single institution, phase II trial

In patients with extensive unresectable CRLM, the majority of whom were previously treated, ***47 %*** *were able to undergo complete resection after combined HAI and systemic therapy.*

Conversion to resection is associated with prolonged survival.

Conversion to Resection



D'Angelica et al *Ann Surg 2015*

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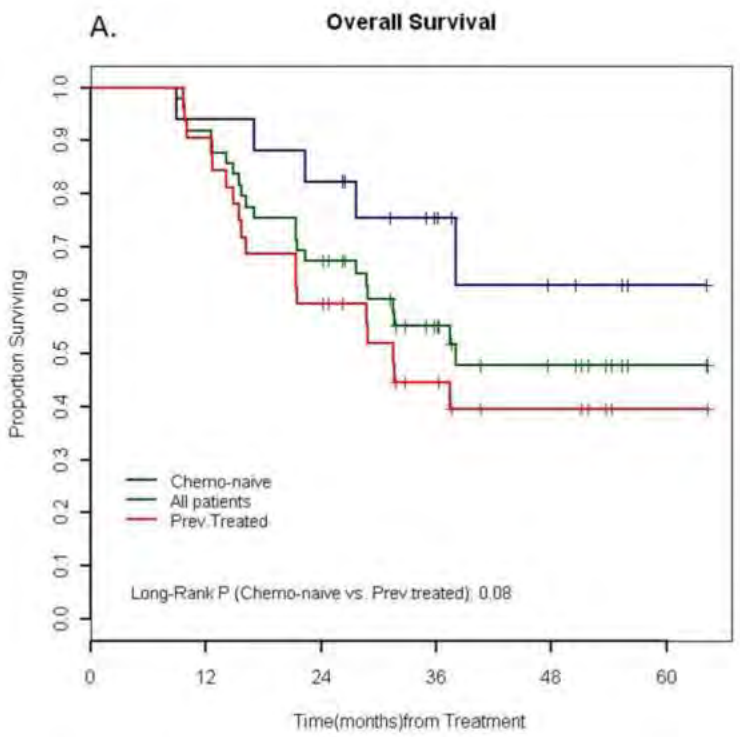
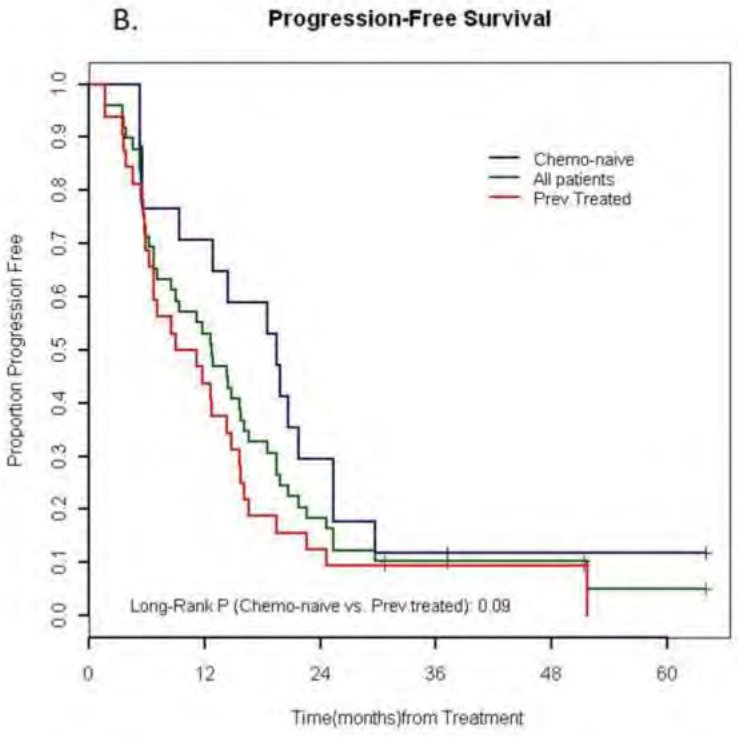
Conversion to Resection





D'Angelica et al *Ann Surg 2015*

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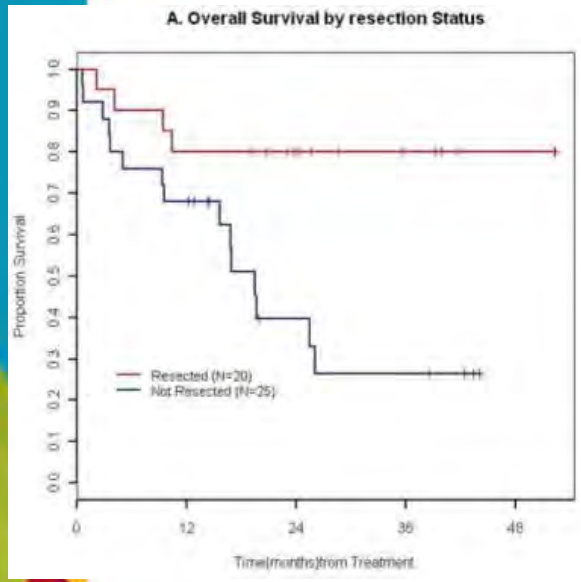
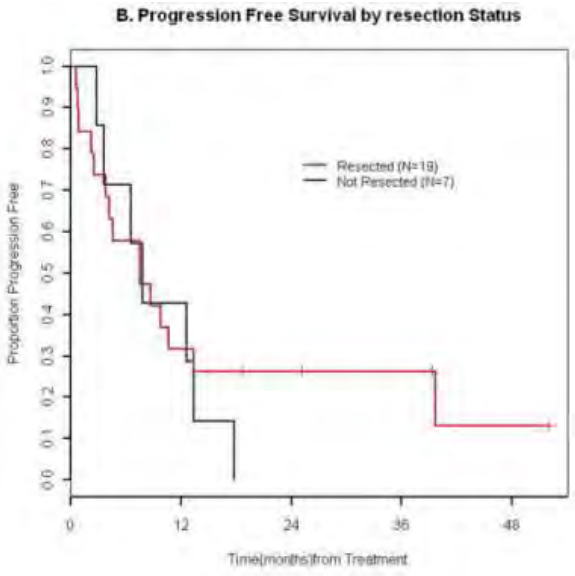
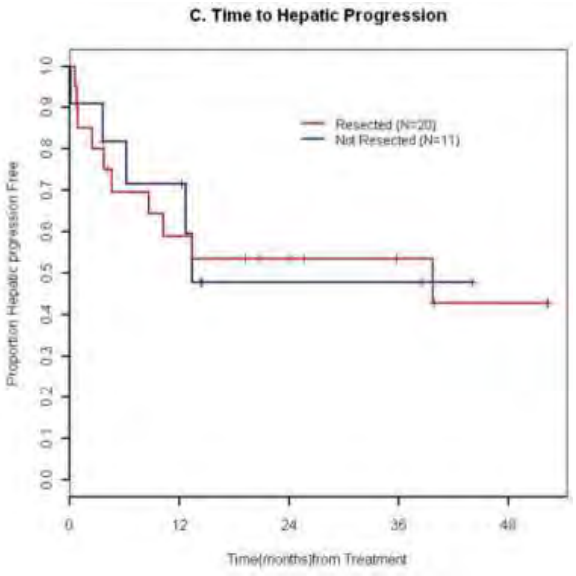
Conversion to Resection







D'Angelica et al *Ann Surg 2015*

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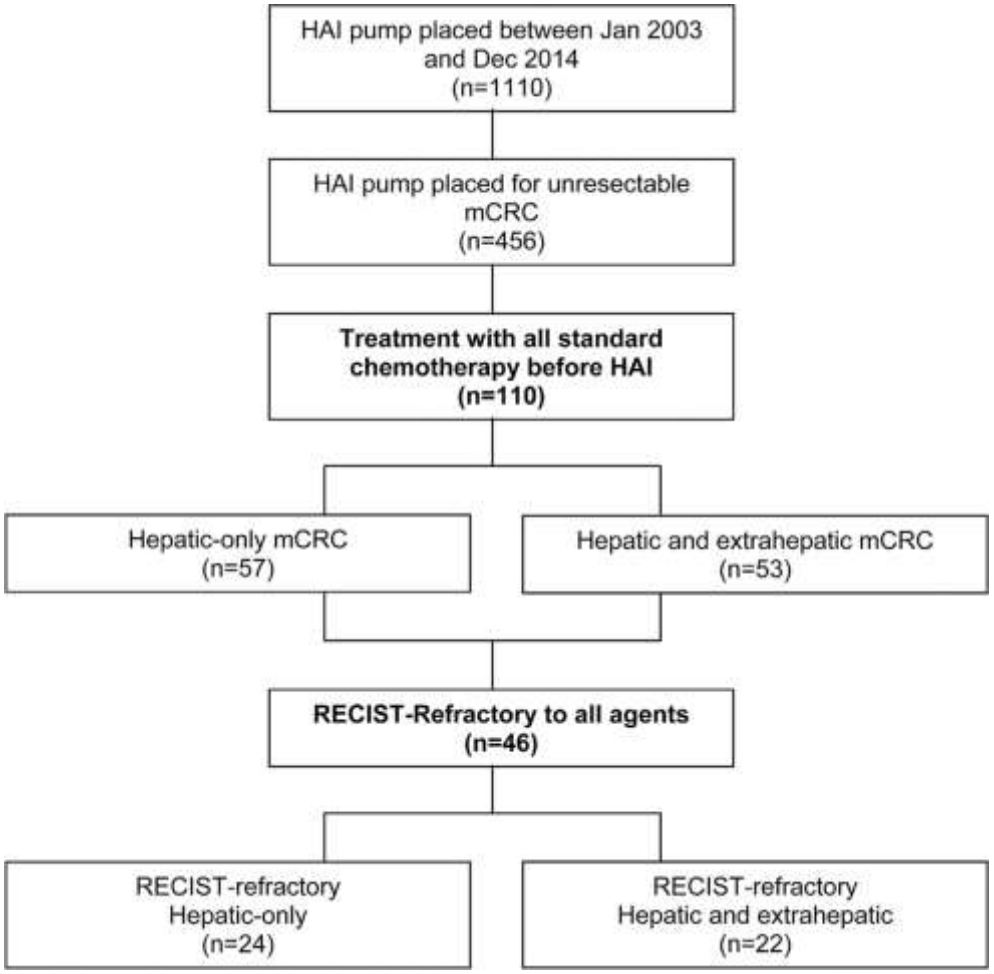
Refractory to Standard Chemotherapy



Cercek et al *J Surg Oncol 2016*

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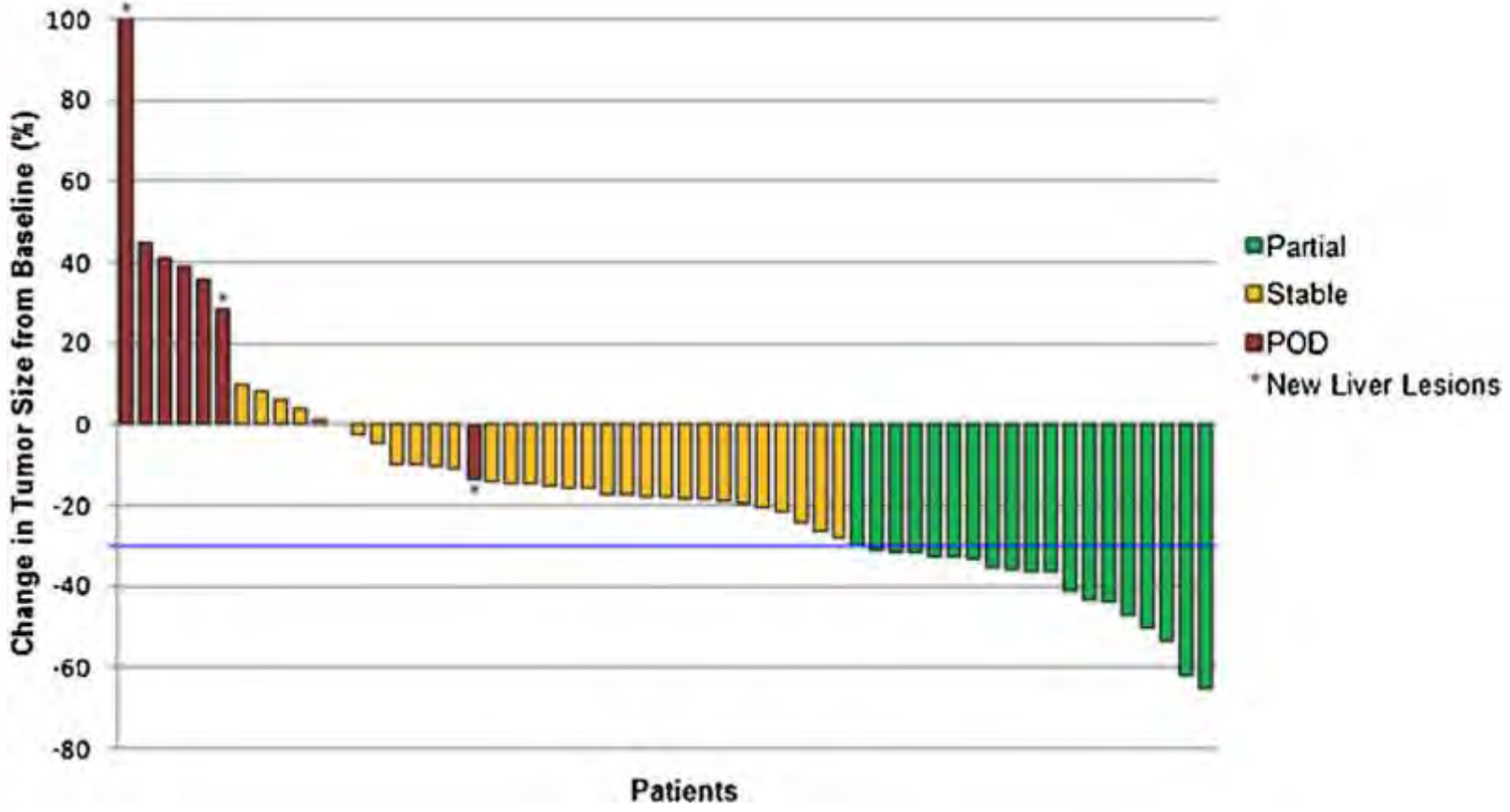
Hepatic Only Disease



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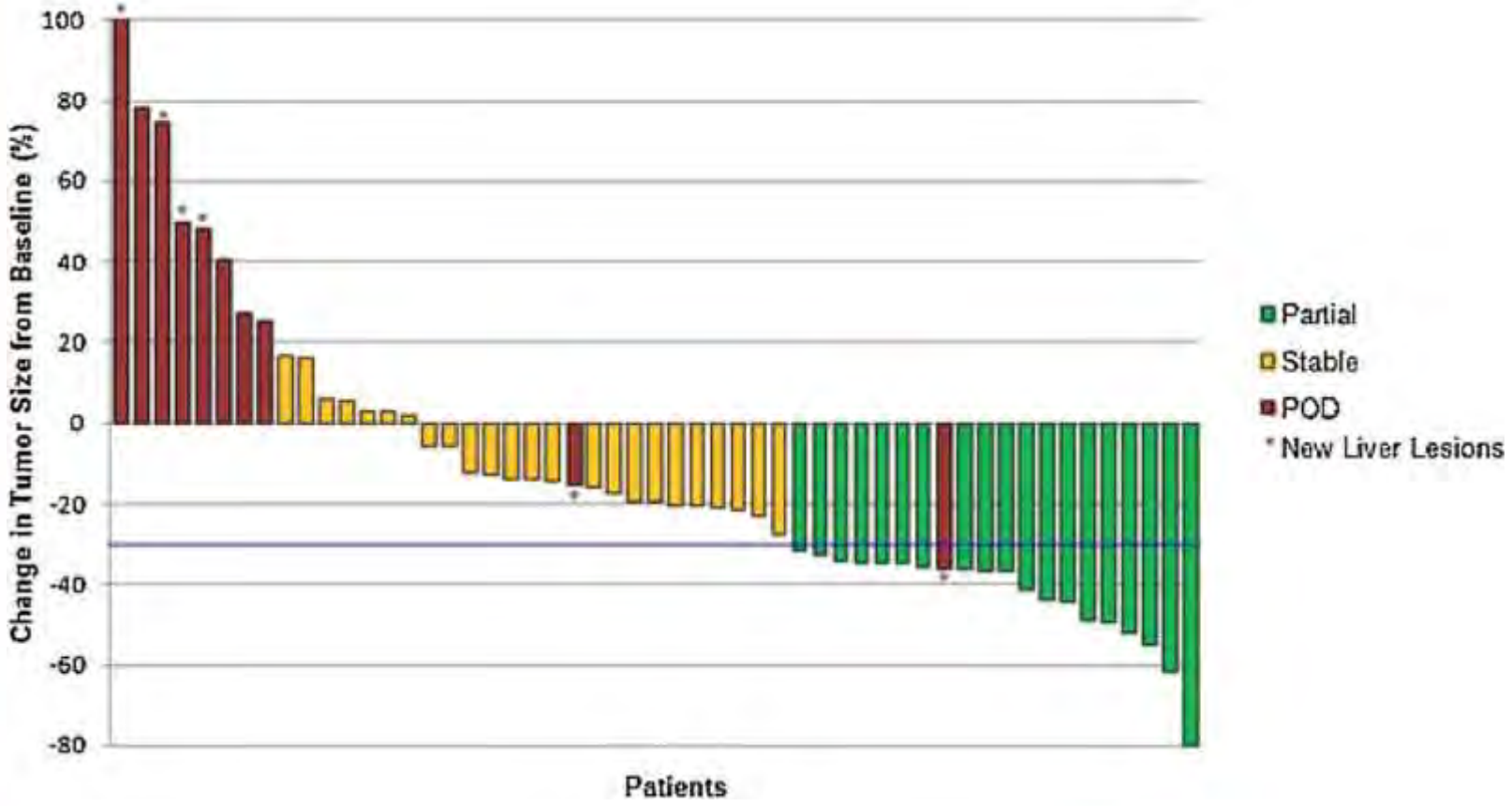
Hepatic and Extra-Hepatic Disease



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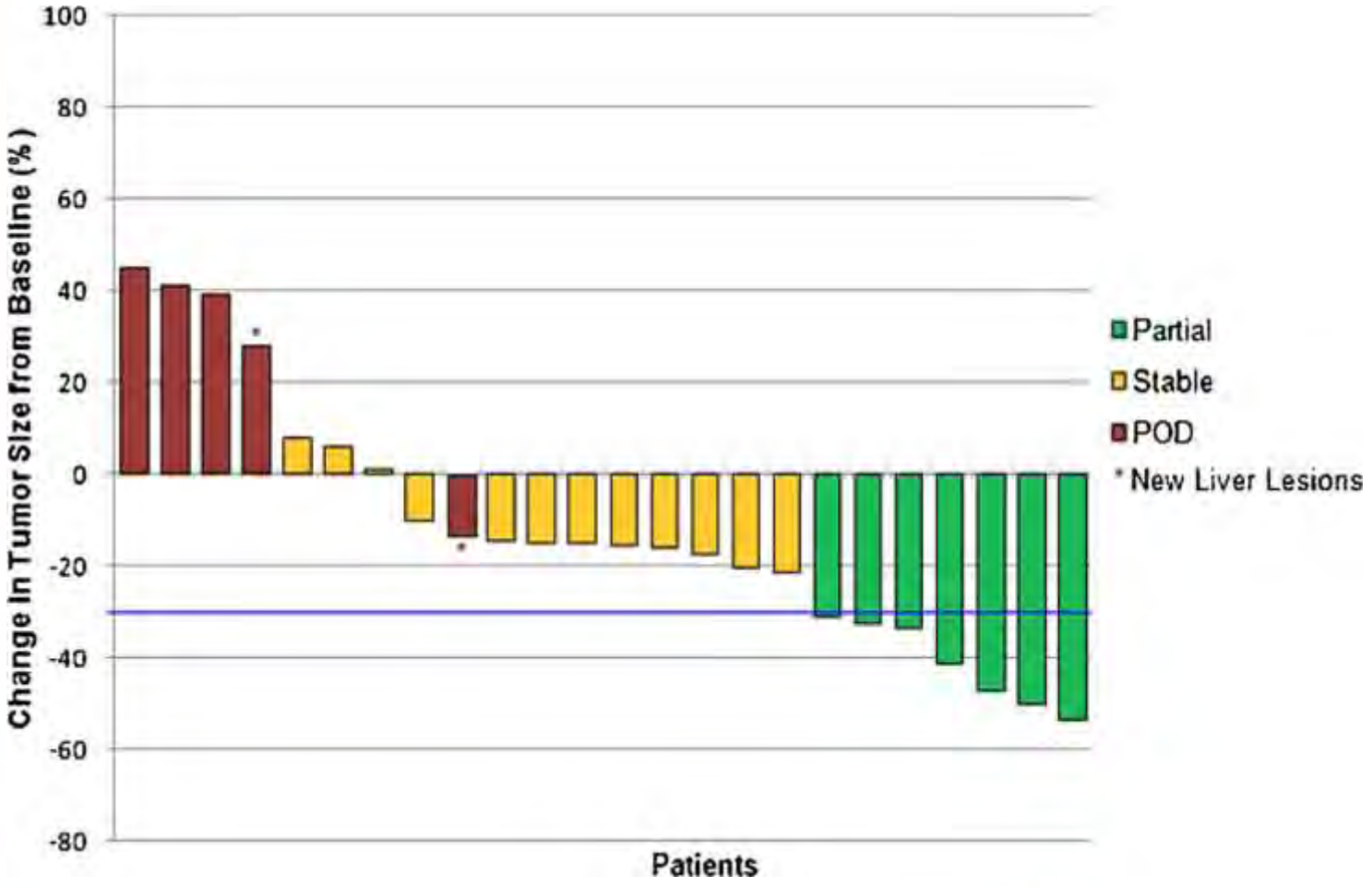
Refractory Hepatic Only Disease



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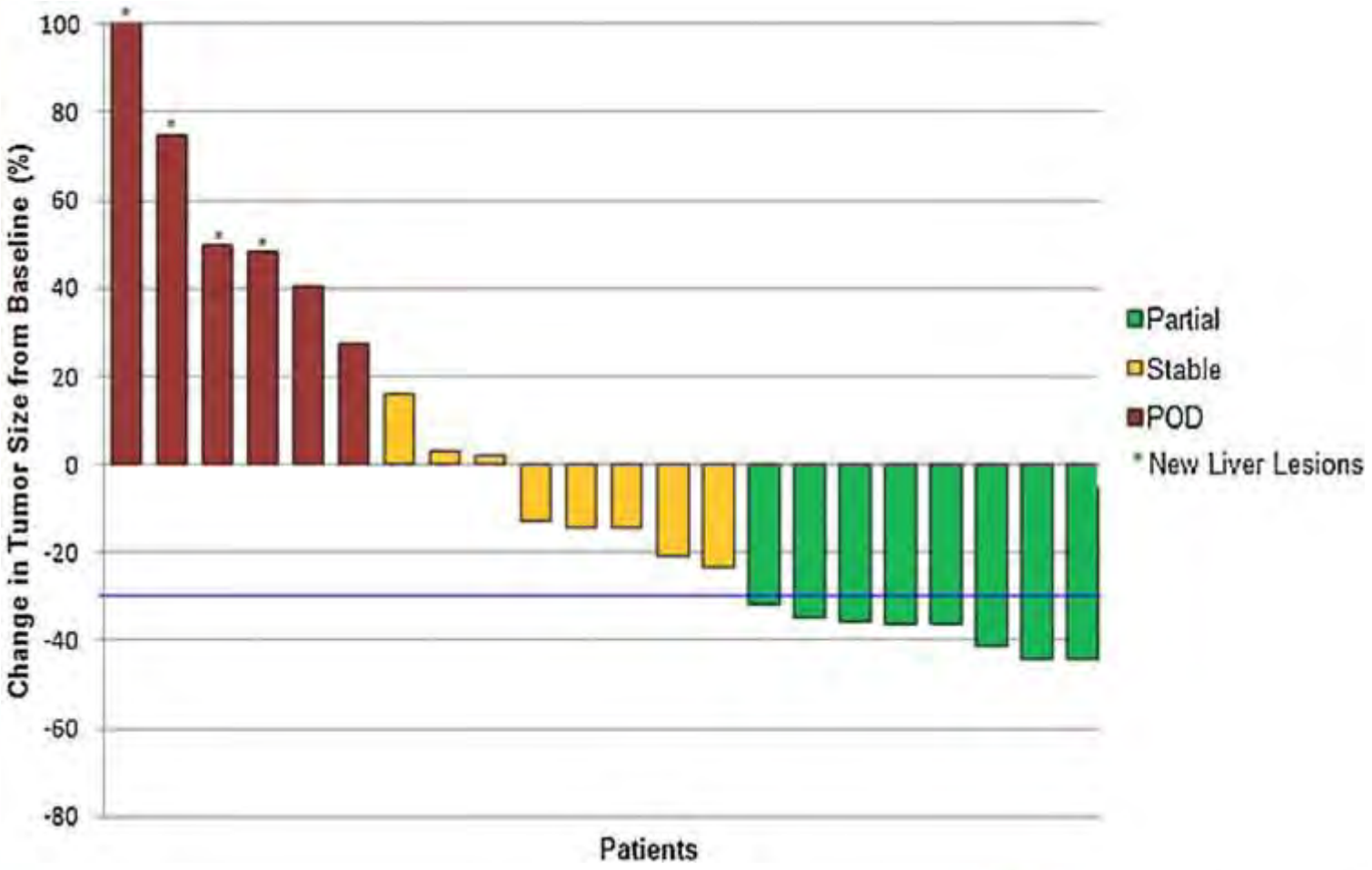
Refractory Hepatic and Extra-Hepatic Disease



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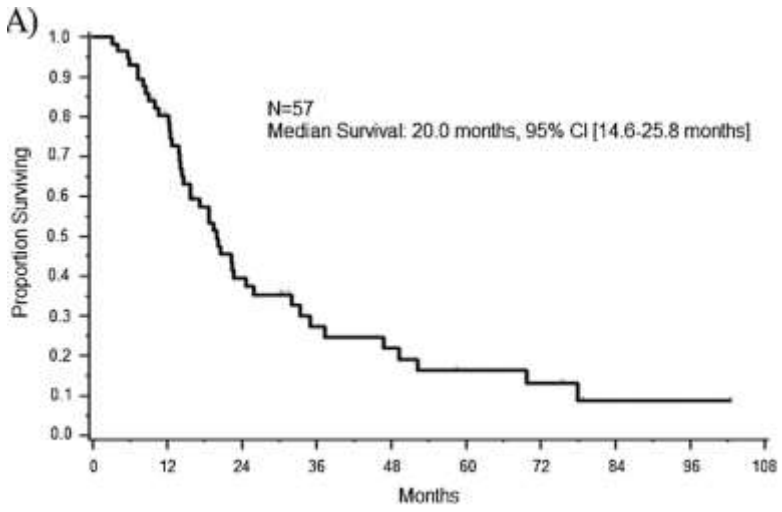
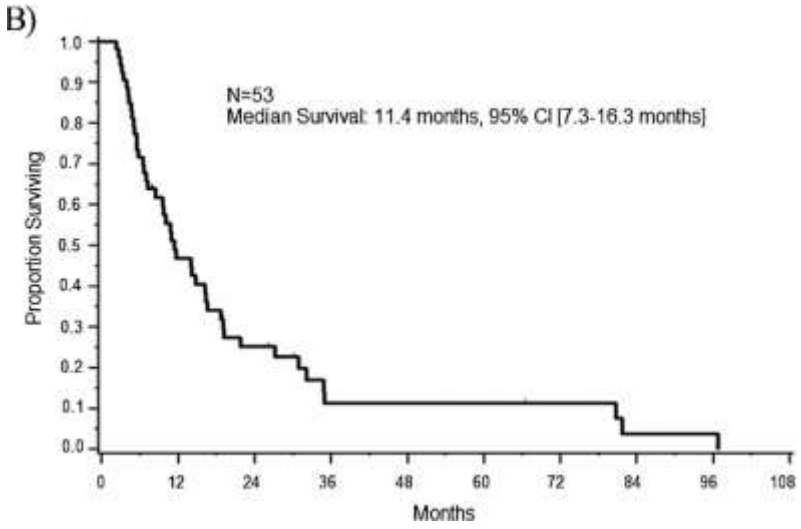
Refractory to Standard Chemotherapy





Hepatic Only Disease:

20 month OS
6 month PFS
7.6 month hPFS

Hepatic and Extrahepatic Disease:

11.4 month OS

Cercek et al *J Surg Oncol 2016*

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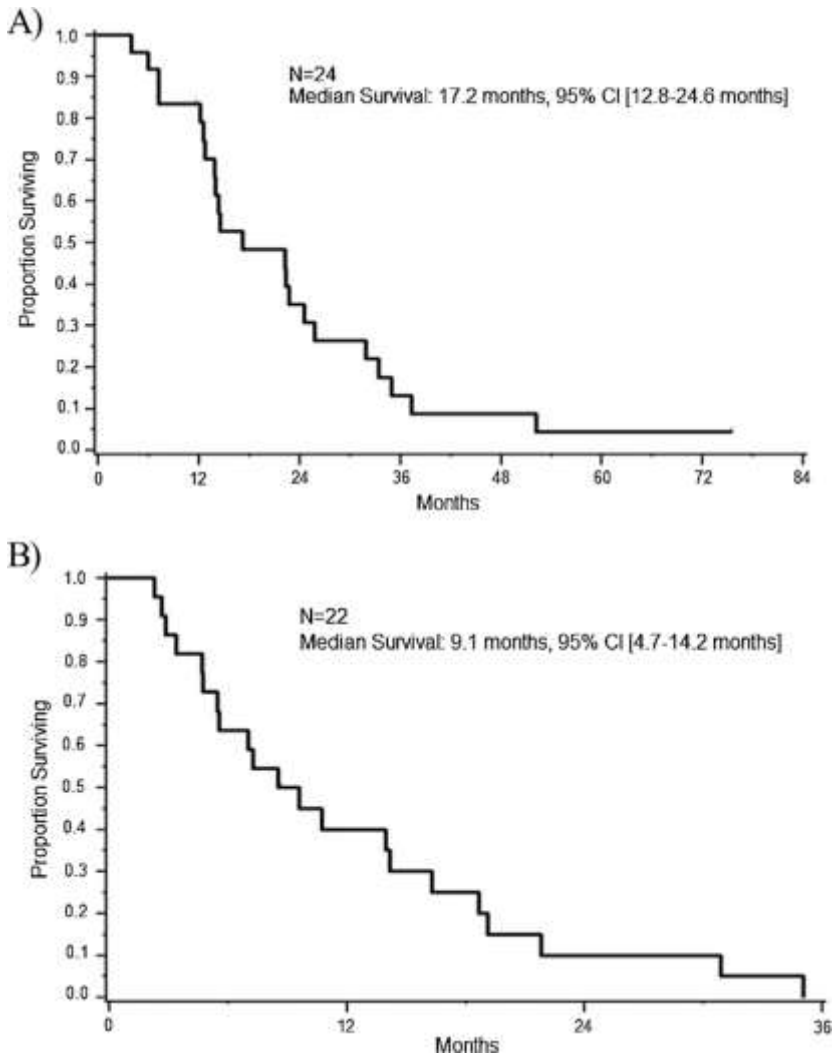
Refractory to Standard Chemotherapy



Hepatic Only Disease:

17.2 month OS

Hepatic and Extrahepatic Disease:

9.1 month OS

Cercek et al *J Surg Oncol 2016*

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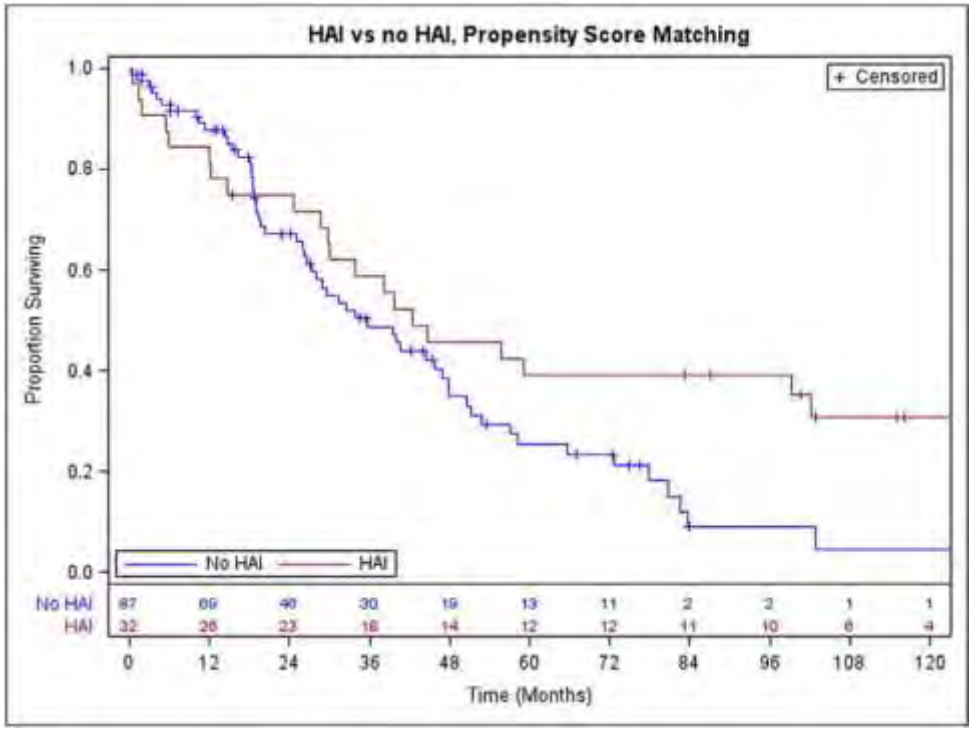
HAI PUMP in Adjuvant Setting



- Retrospective study looking at HAI-pump placement use after hepatic resection
- Median 4 cycles administered
- HAI Group – OS 47 mo
- No HAI Group – OS 37 mo.

Chouliaras et al *HPB 2020*

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HAI Pump Centers

HAI Consortium Research Network

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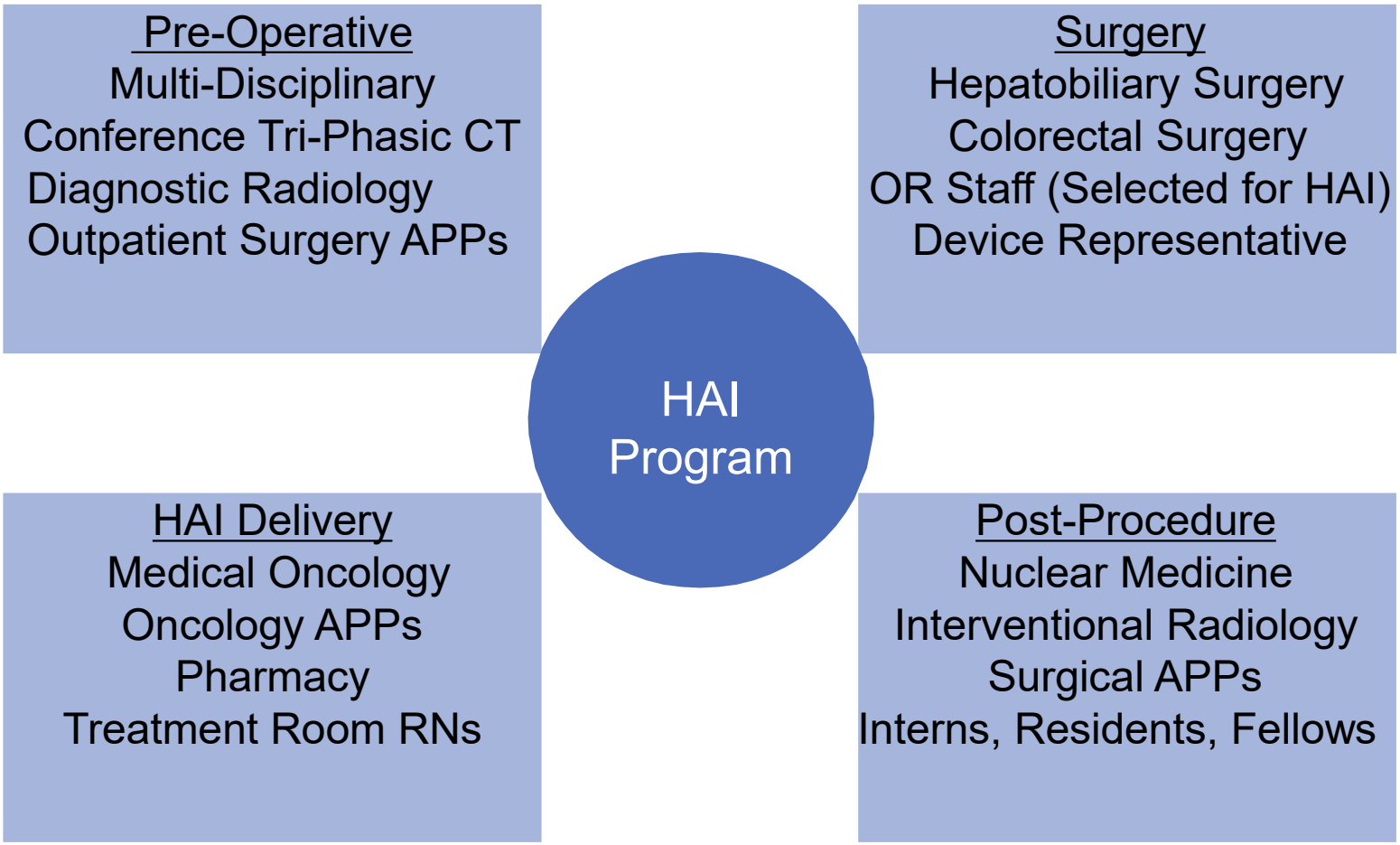

Lidsky et al *Ann Surg Oncol 2020*

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ECOG-ACRIN cancer research group

EA2222 - A Randomized Phase III Study of Systemic Therapy With or Without Hepatic Arterial Infusion for Unresectable Colorectal Liver Metastases: The PUMP Trial

Study Chair: Michael Lidsky, MD

Patient Eligibility

Adults, 18-80 years old

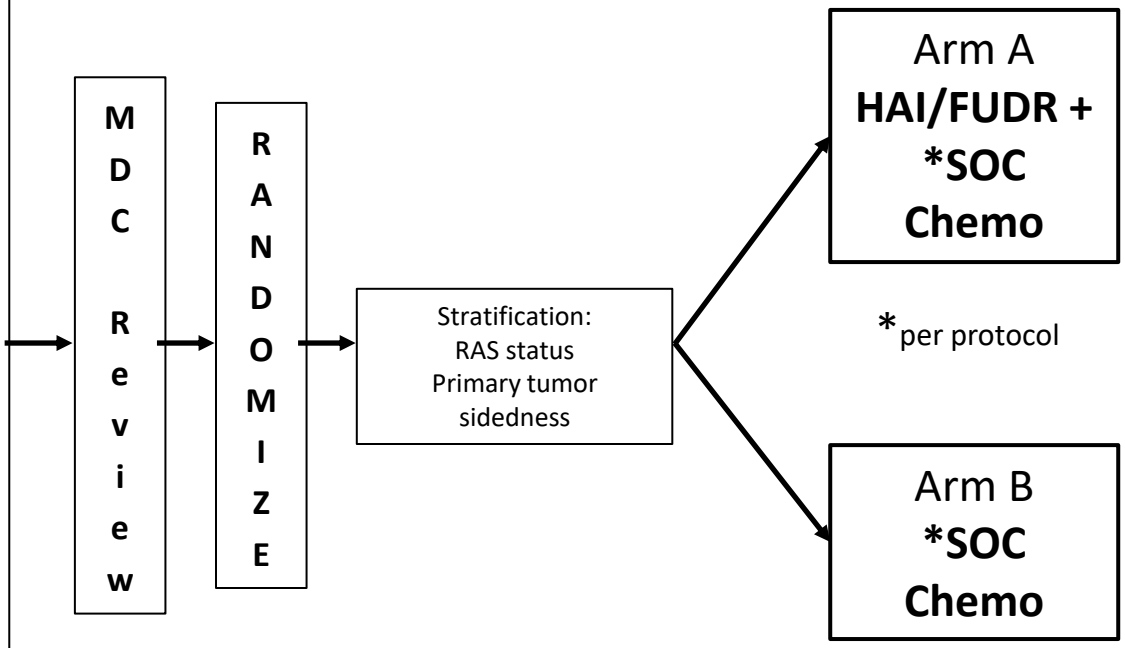
Persistently and technically unresectable liver-only metastatic CRC

(Allowed: Any calcified pulmonary nodule or ≤ 5 pulmonary nodules ≤ 6 mm and stable for ≥ 3 months on chemotherapy)

Prior systemic chemotherapy

3 – 6 months of 1st line chemo

New CRLM < 12 months after completing adjuvant therapy for stage II-III CRC



*per protocol

Primary endpoint = OS

Secondary endpoints: PFS, hPFS, ePFS, ORR, Conversion to resection, Toxicity

Correlatives – to improve patient selection and identify which patients may be at risk for short vs long term complications

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