City of Hope

ANNUAL

Advances and Innovations in Endoscopic Oncology and Multidisciplinary Gastrointestinal Cancer Care

Revolutionizing Survival: Surgical Breakthroughs in Liver Directed Therapies for Colorectal Cancer

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Disclosures

- I do not have any relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

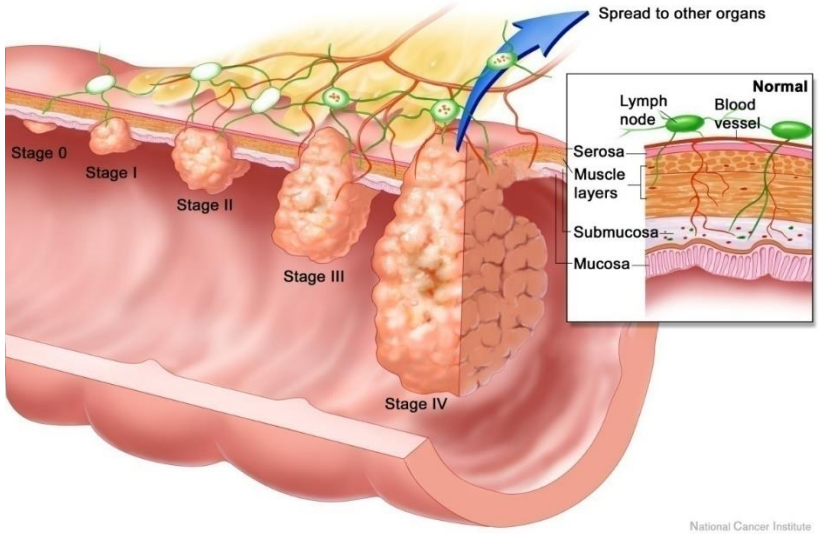
Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- XXX
- XXXX

Colorectal Liver Metastases

Natural History



Colon & Rectal Cancer
153,000 New Cases

- **20-30%** Synchronous Liver Mets
- **70- 80%** No Liver Mets
  - **25%** Liver Mets

40-50%

- **Untreated** <1% Alive 5 yrs
- **Chemo + Sx** >60% Alive 5 yr

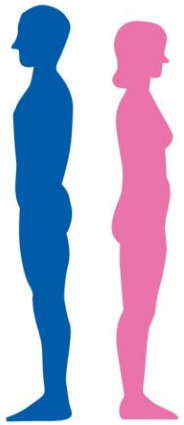
Incidence: Cancer Statistics

Cancer statistics, 2024

#3

Estimated New Cases

	Males			Females	
	Prostate	299,010	29%	Breast	310,720	32%
	Lung & bronchus	116,310	11%	Lung & bronchus	118,270	12%
←	Colon & rectum	81,540	8%	Colon & rectum	71,270	7% ←
	Urinary bladder	63,070	6%	Uterine corpus	67,880	7%
	Melanoma of the skin	59,170	6%	Melanoma of the skin	41,470	4%
	Kidney & renal pelvis	52,380	5%	Non-Hodgkin lymphoma	36,030	4%
	Non-Hodgkin lymphoma	44,590	4%	Pancreas	31,910	3%
	Oral cavity & pharynx	41,510	4%	Thyroid	31,520	3%
	Leukemia	36,450	4%	Kidney & renal pelvis	29,230	3%
	Pancreas	34,530	3%	Leukemia	26,320	3%
	All sites	**1,029,080**		**All sites**	**972,060**	

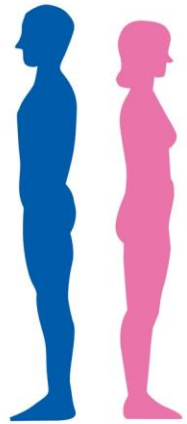


Colon & Rectal Cancer
152, 810 New Cases

CRLM ≈50%
71, 405

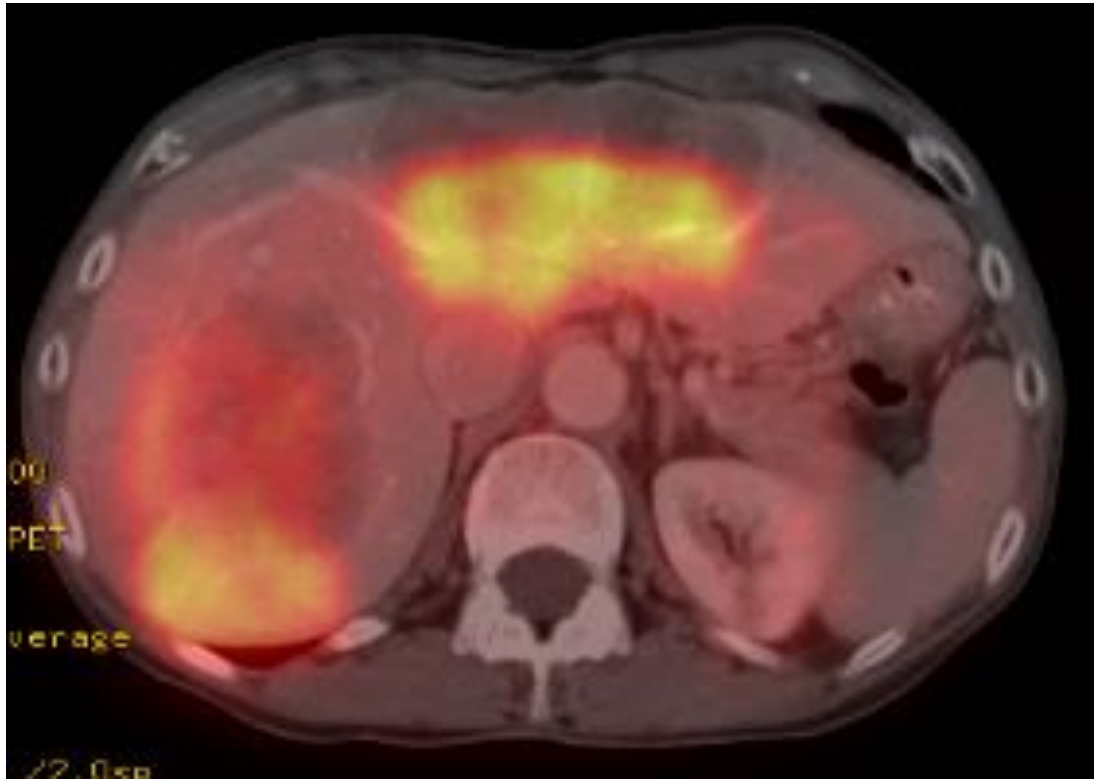
Estimated Deaths

	Males			Females	
	Lung & bronchus	65,790	20%	Lung & bronchus	59,280	21%
	Prostate	35,250	11%	Breast	42,250	15%
←	Colon & rectum	28,700	9%	Pancreas	24,480	8%
	Pancreas	27,270	8%	Colon & rectum	24,310	8% ←
	Liver & intrahepatic bile duct	19,120	6%	Uterine corpus	13,250	5%
	Leukemia	13,640	4%	Ovary	12,740	4%
	Esophagus	12,880	4%	Liver & intrahepatic bile duct	10,720	4%
	Urinary bladder	12,290	4%	Leukemia	10,030	3%
	Non-Hodgkin lymphoma	11,780	4%	Non-Hodgkin lymphoma	8,360	3%
	Brain & other nervous system	10,690	3%	Brain & other nervous system	8,070	3%
	All sites	**322,800**		**All sites**	**288,920**	



American Cancer Society

Resectable or Unresectable?



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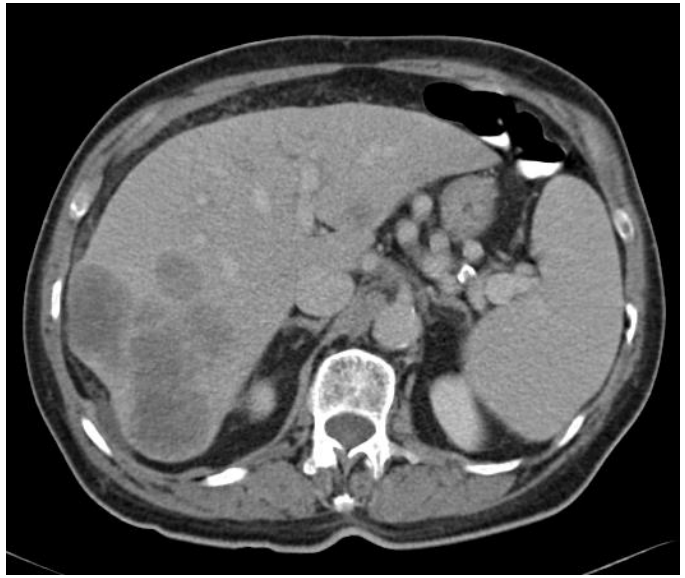
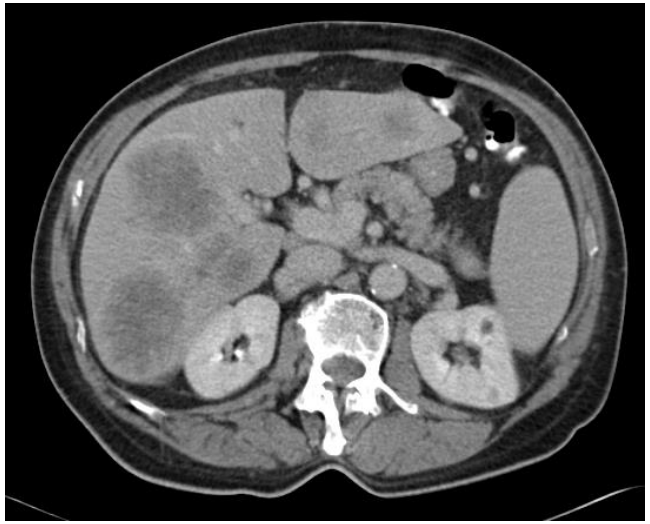
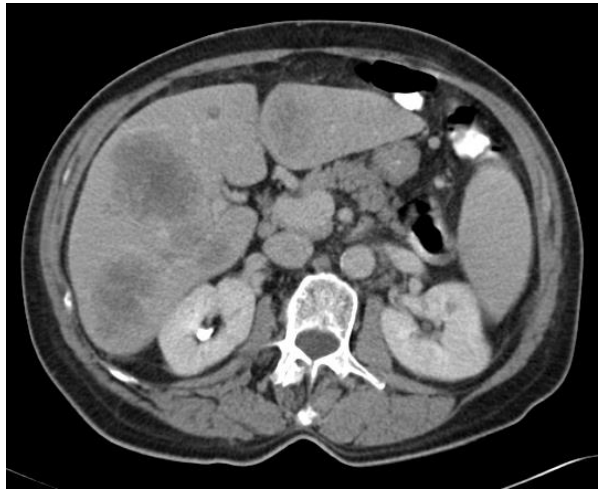
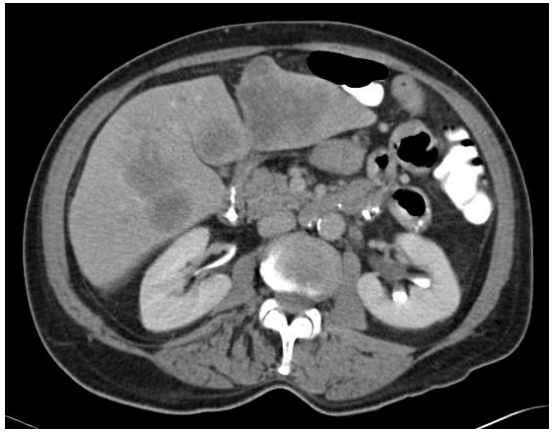
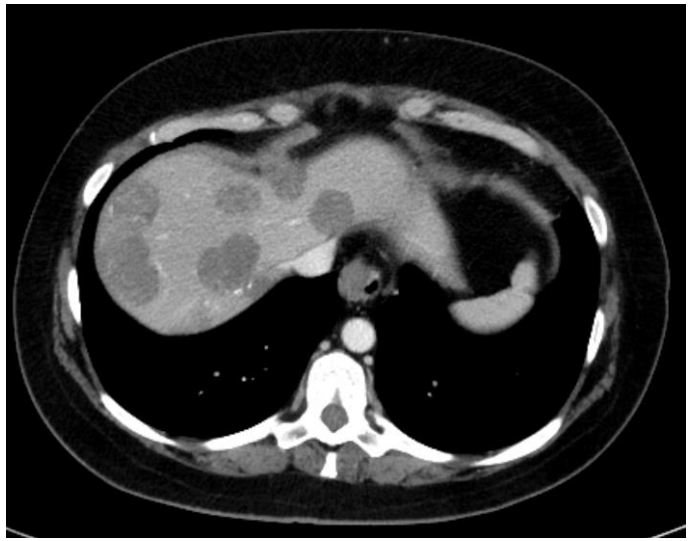
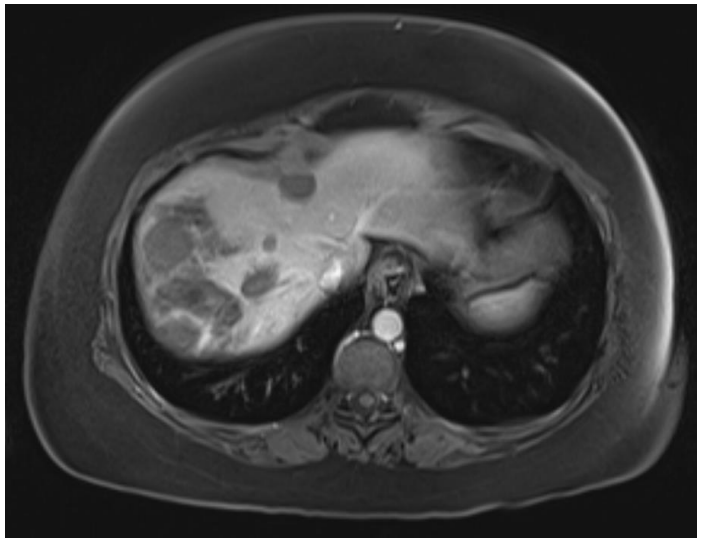





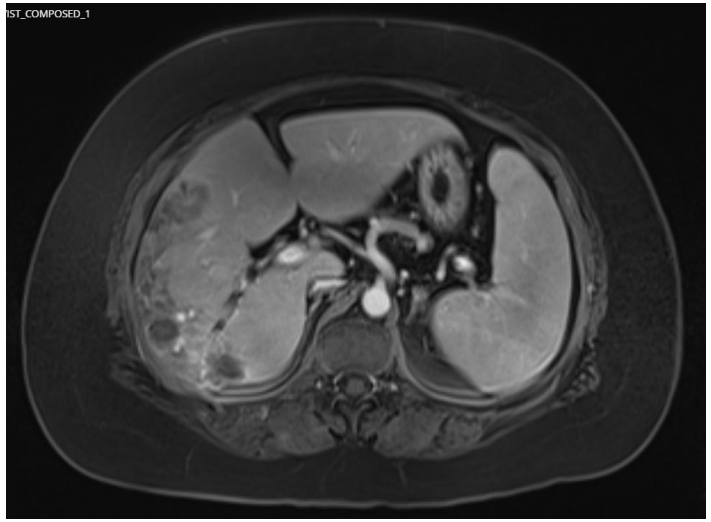
Resectable or Unresectable?

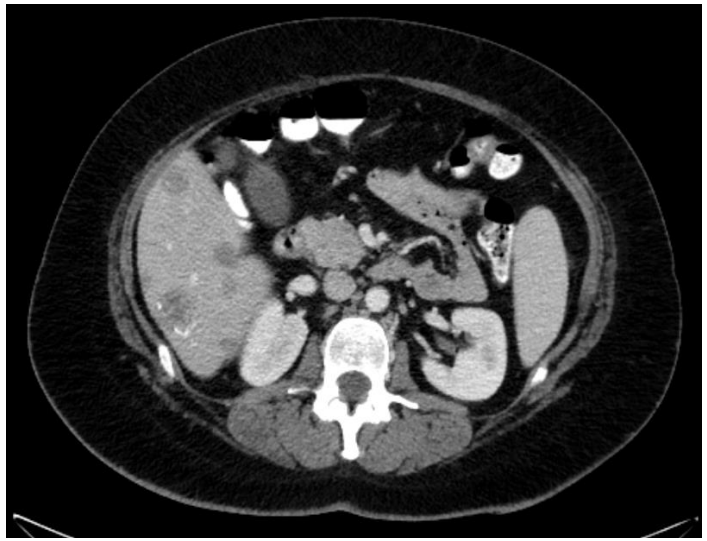
10/22/12

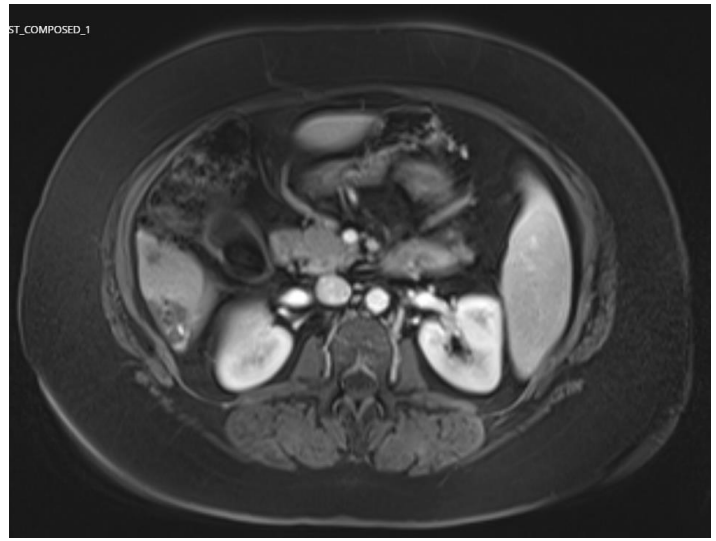
Resectable or Unresectable?











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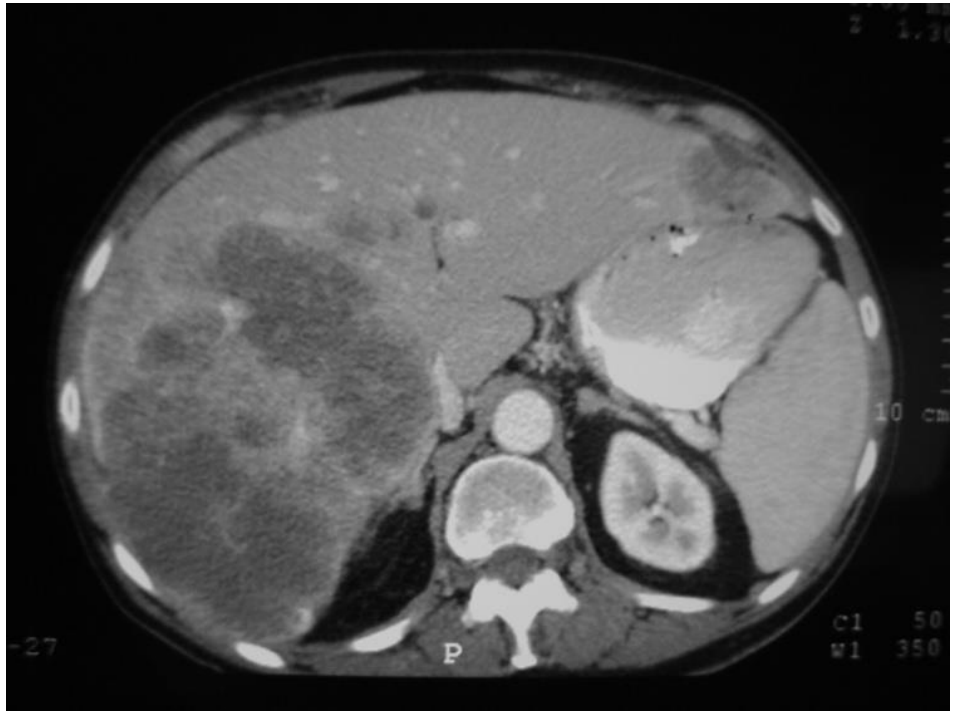
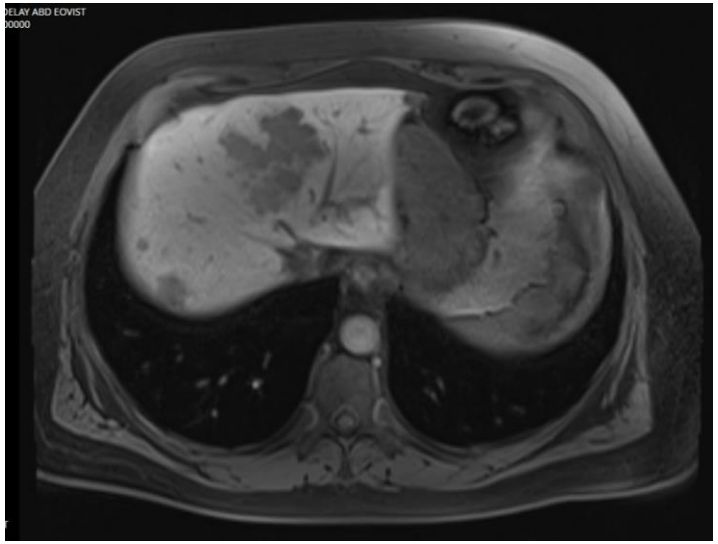
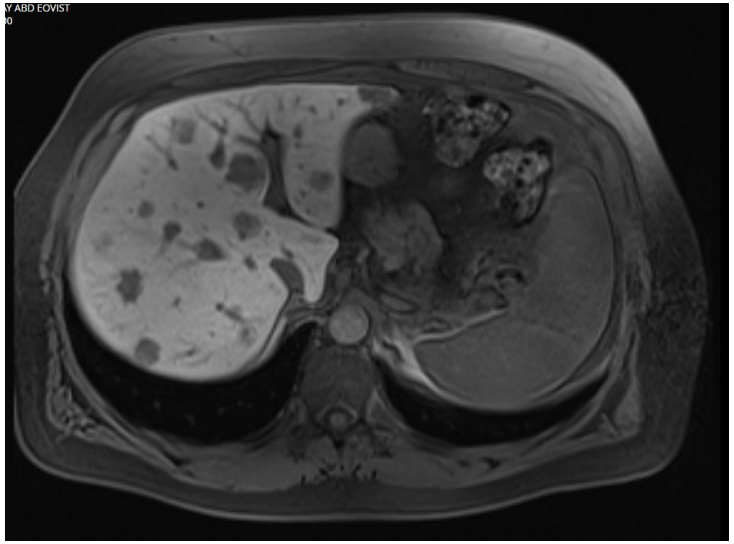


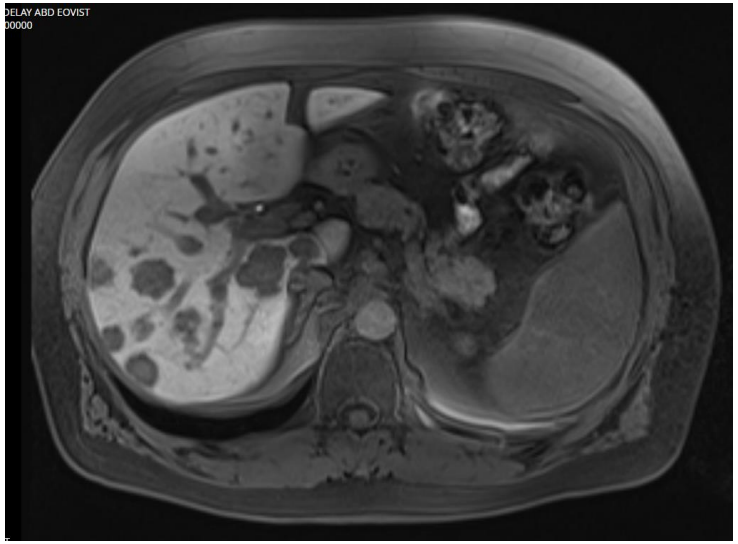
Resectable or Unresectable?

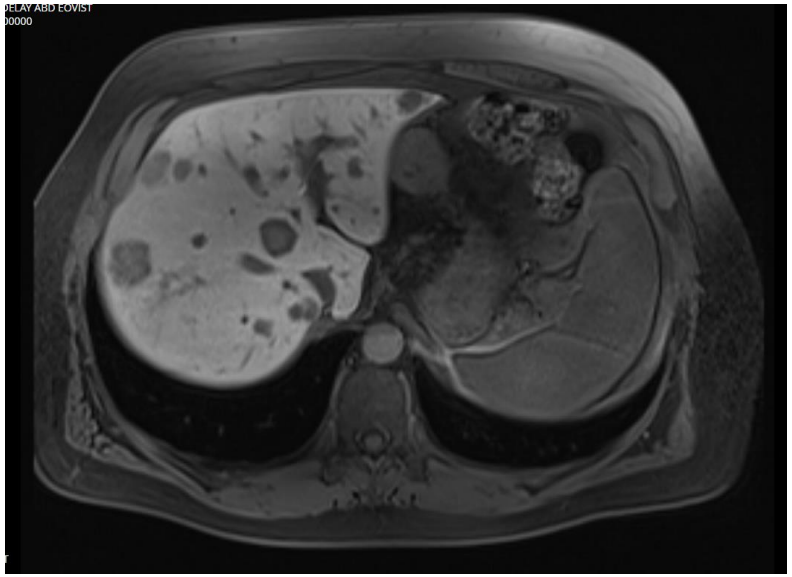
09/23/15

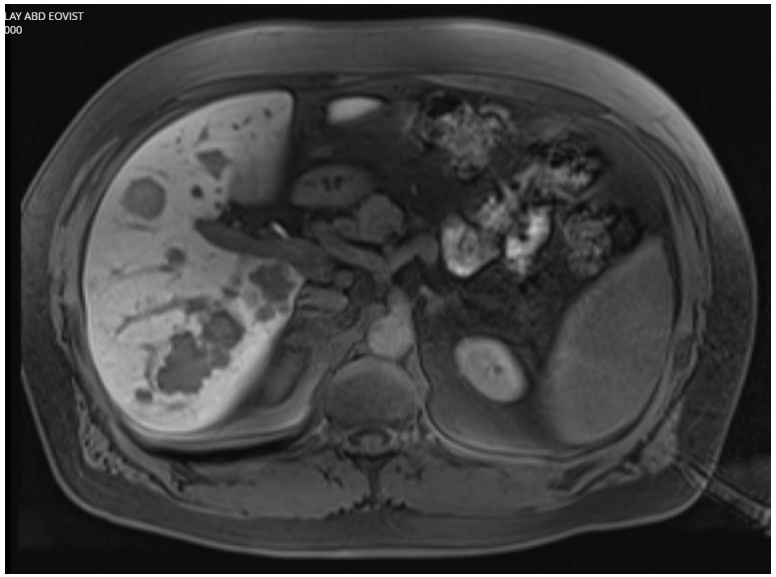
Distinct Entity of Liver Dominant Dz

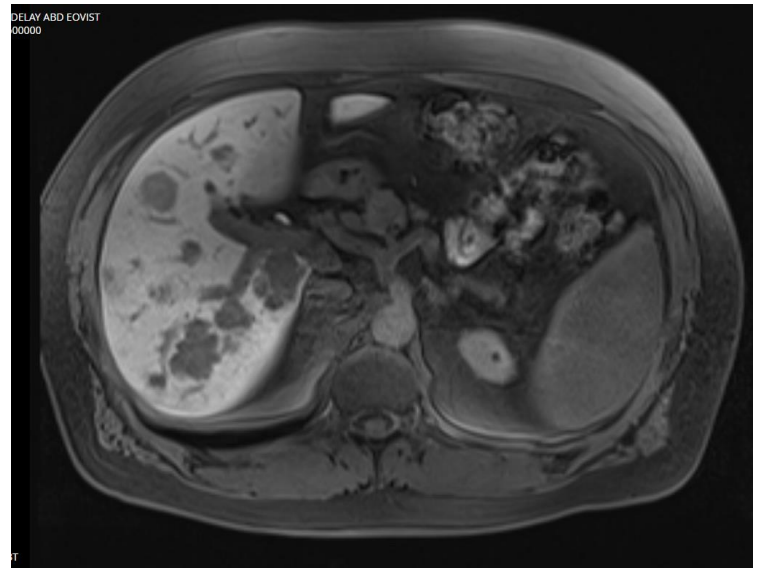












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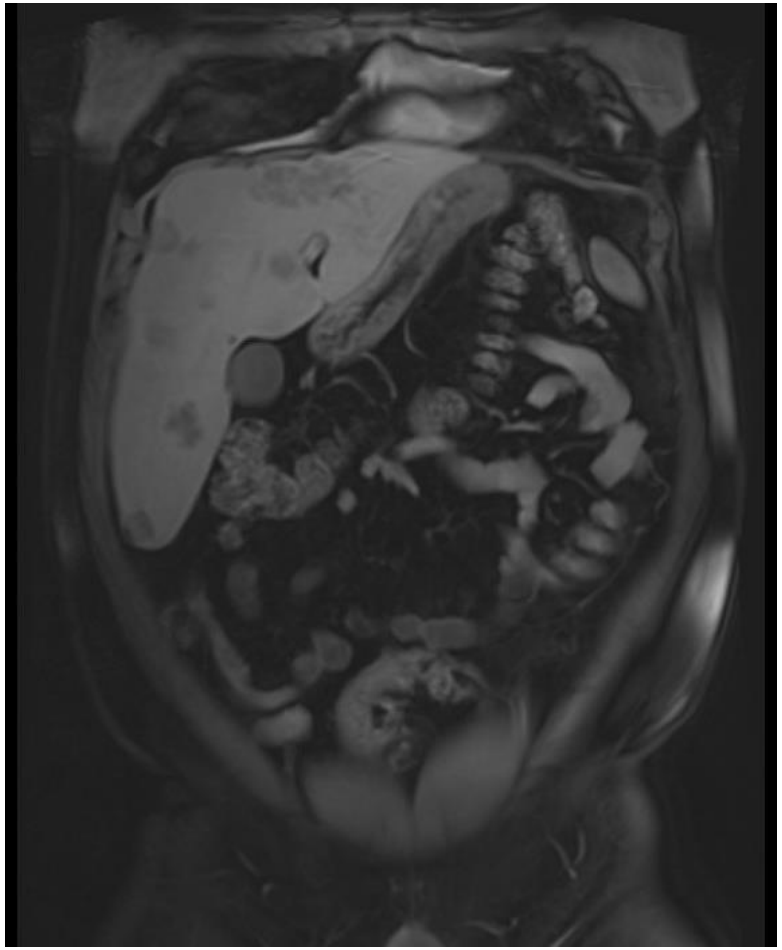
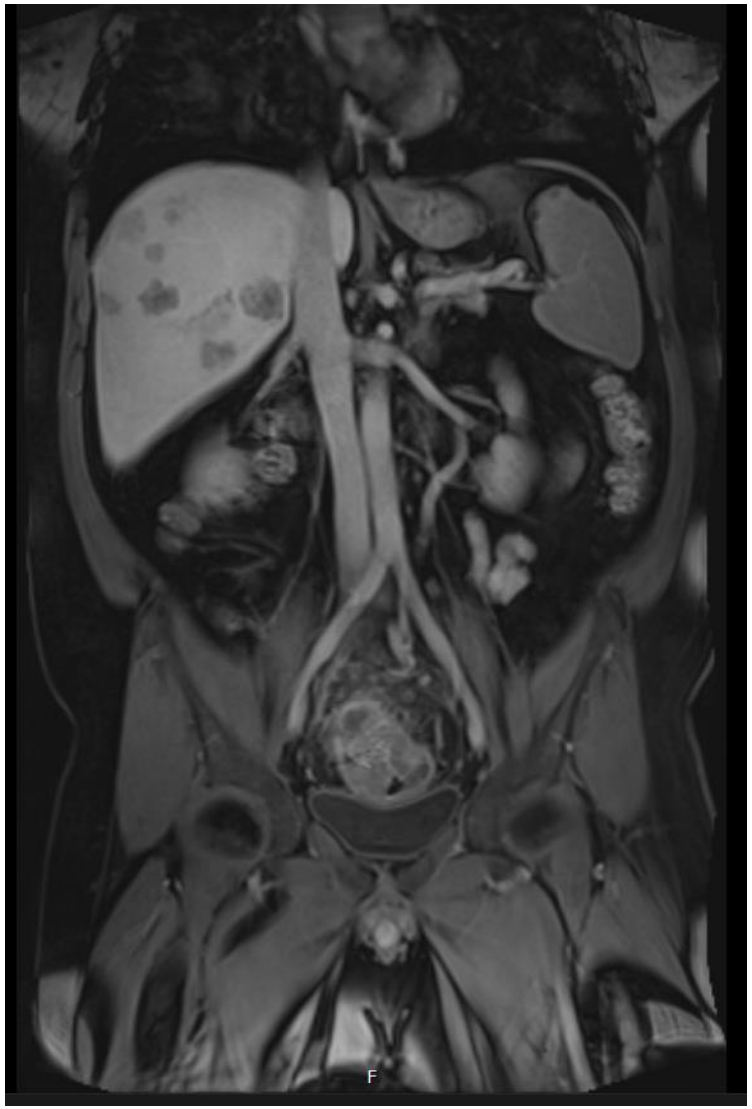
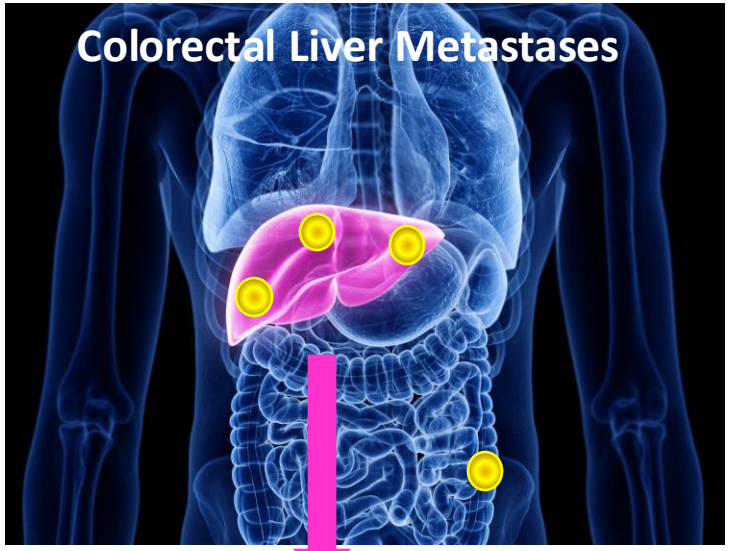




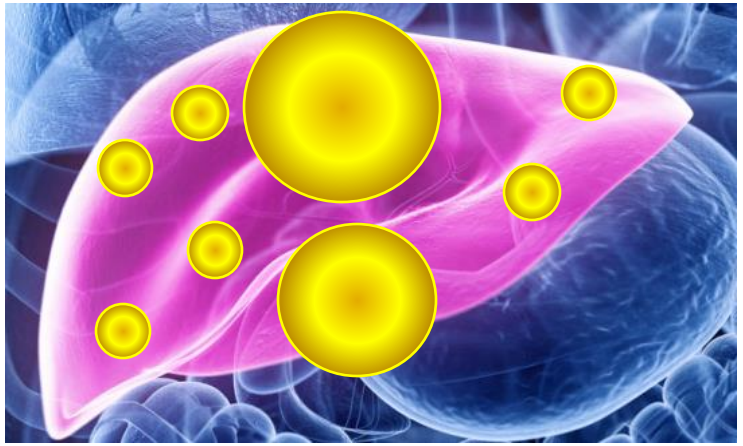
Types of Colorectal Liver Metastases



RESECTABLE≤ 20%

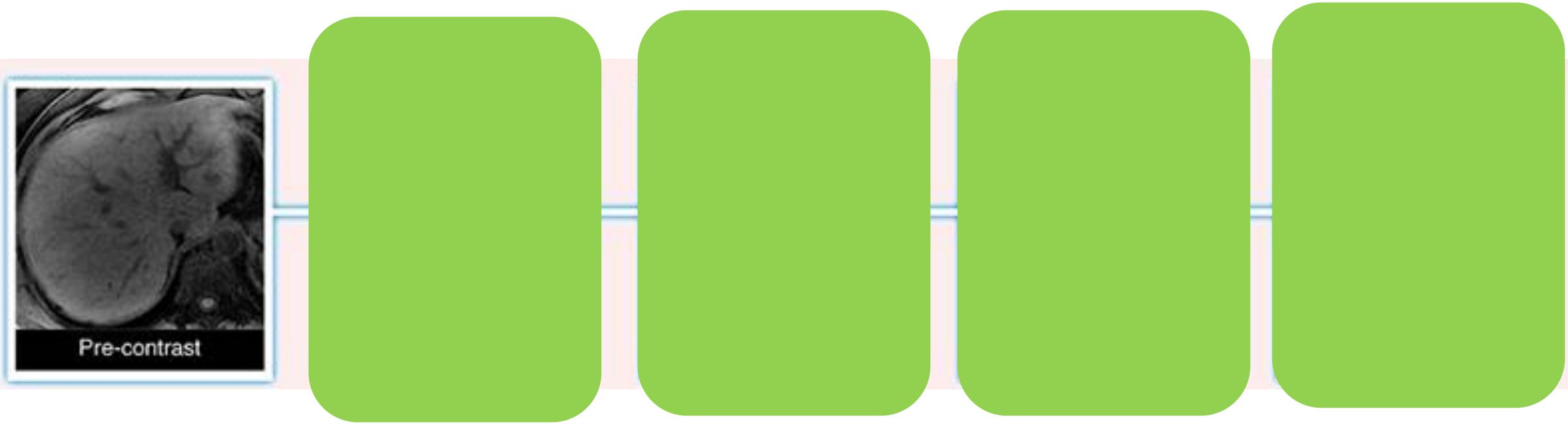
BORDERLINE RESECTABLE= 30-50%

UNRESECTABLE= 30-50%



CT Scan is always Good- BUT Nothing like a great MRI with EOVIST

PET is meaningless for Anatomic Imaging- Great for Extrahepatic Disease

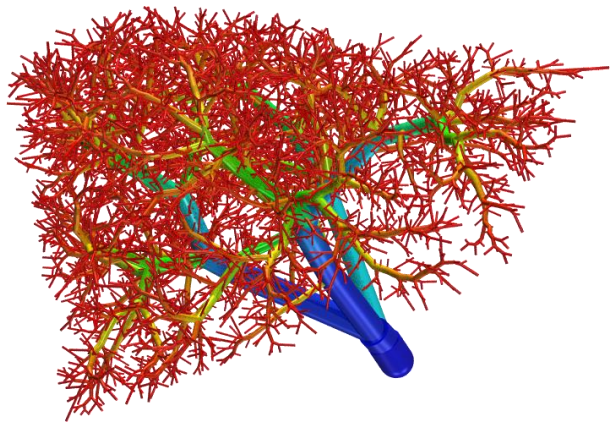


Attiyeh MA……**Singh G**. *Cancers. 2023 Oct 23;15(20):5109.*

Hepatic Veins- 3D

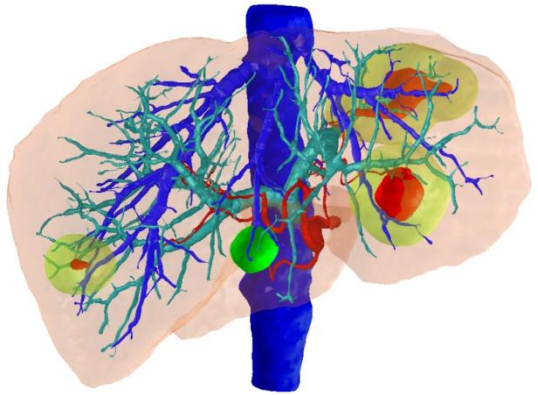
7m

Challenges of Liver Surgery



Anatomical Challenges

- No Bloodless plane exists
- It's deceptive surface anatomy leads into rather than away from the its largest vessels
- Complex inflow and outflow tracts cross at right angles



Metabolic- Post Chemo

- Histologic Simplicity belies its Metabolic Complexity
- It has been one of the last organs to yield to the rapid surgical advances made in the 19th century

Greek Mythology- Prometheus

Regeneration of the Liver

Prometheus had stolen fire from **Zeus** and given it to the mortals in their dark caves.
He had **Hepheistos** shackle Prometheus to the side of a crag, high in the **Caucasus mountains**.
Each day, Prometheus would be tormented by **Zeus' eagle** as it tore at his immortal flesh and tried to devour his liver. Each night, as the frost bit it's way into his sleep, the torn flesh would mend so the eagle could begin anew at the first touch of Dawn.

With A Little Help From My Friends

Unresectable → Resectable

Radiation Oncologist

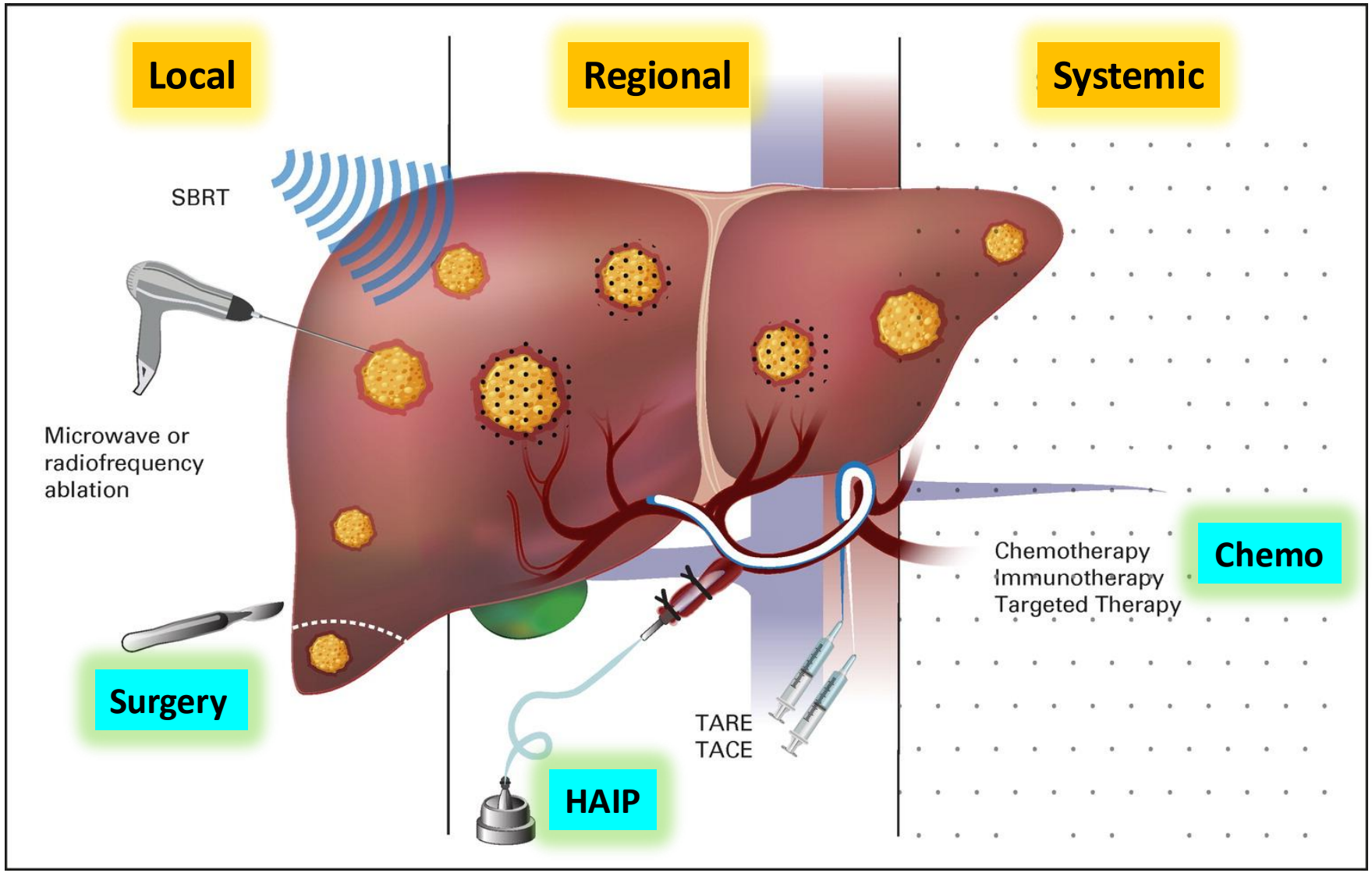
Medical Oncologist

Regenerative Potential

Interventional Radiologist

Management Modalities for Colorectal Liver Metastases

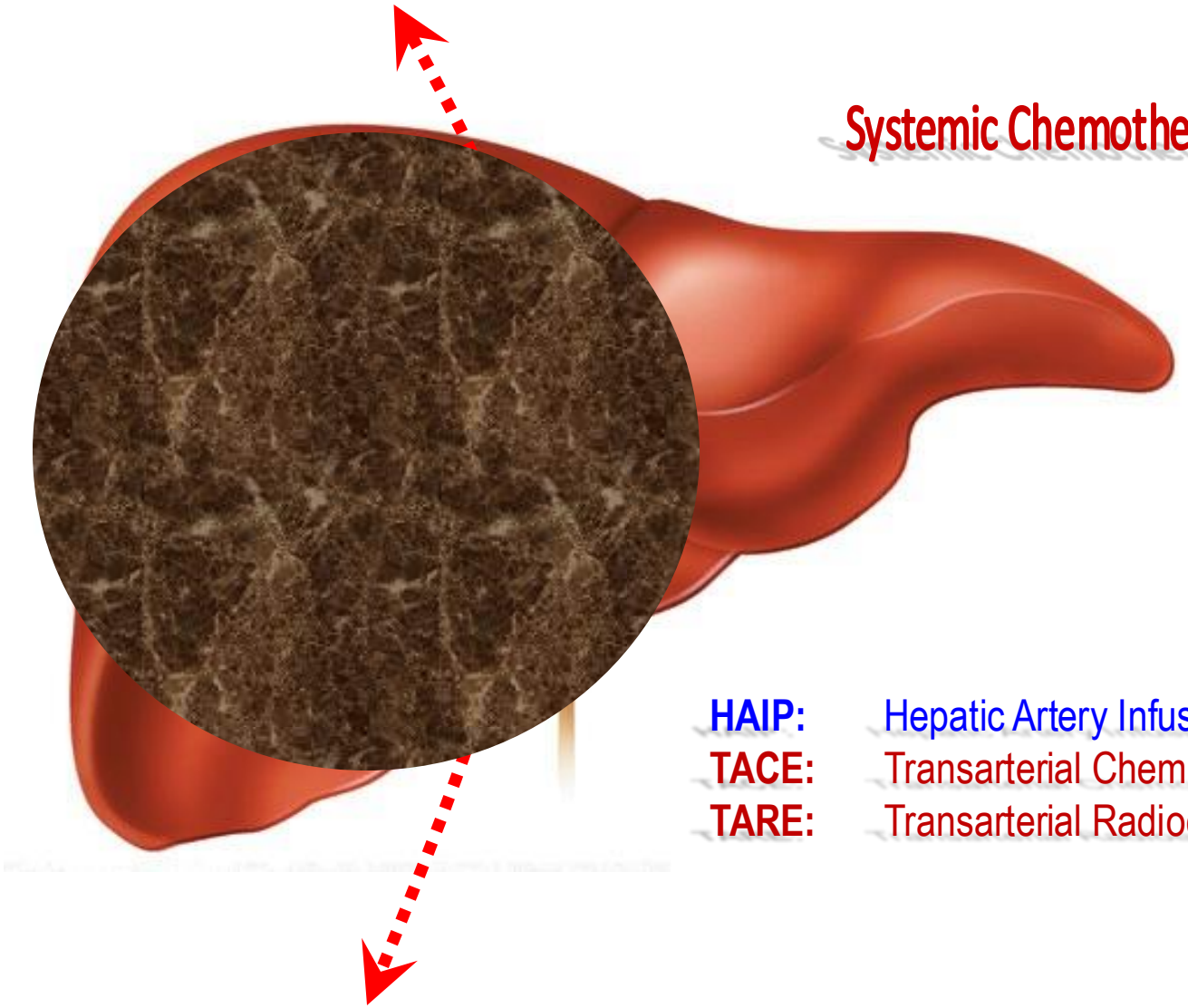
What to use and when?



IRE- Nanoknife
Cryotherapy
~~Ethanol Injection~~
~~Gene Therapy~~
Transplant

Designing Liver Resections

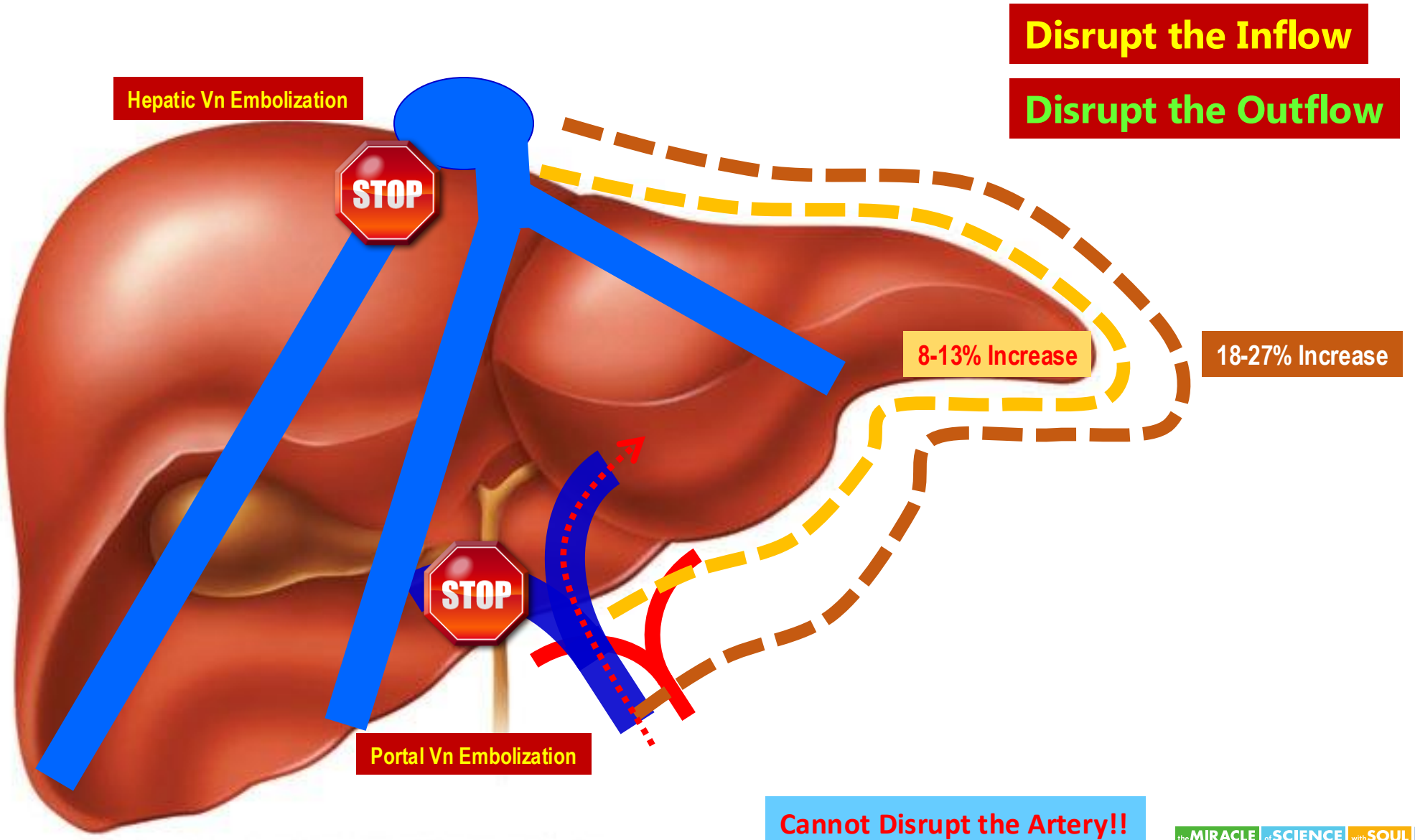
Strategy : Inducing Shrinkage



HAIP: Hepatic Artery Infusion Pump
TACE: Transarterial Chemoembolization
TARE: Transarterial Radioembolization Y90- SirFlox

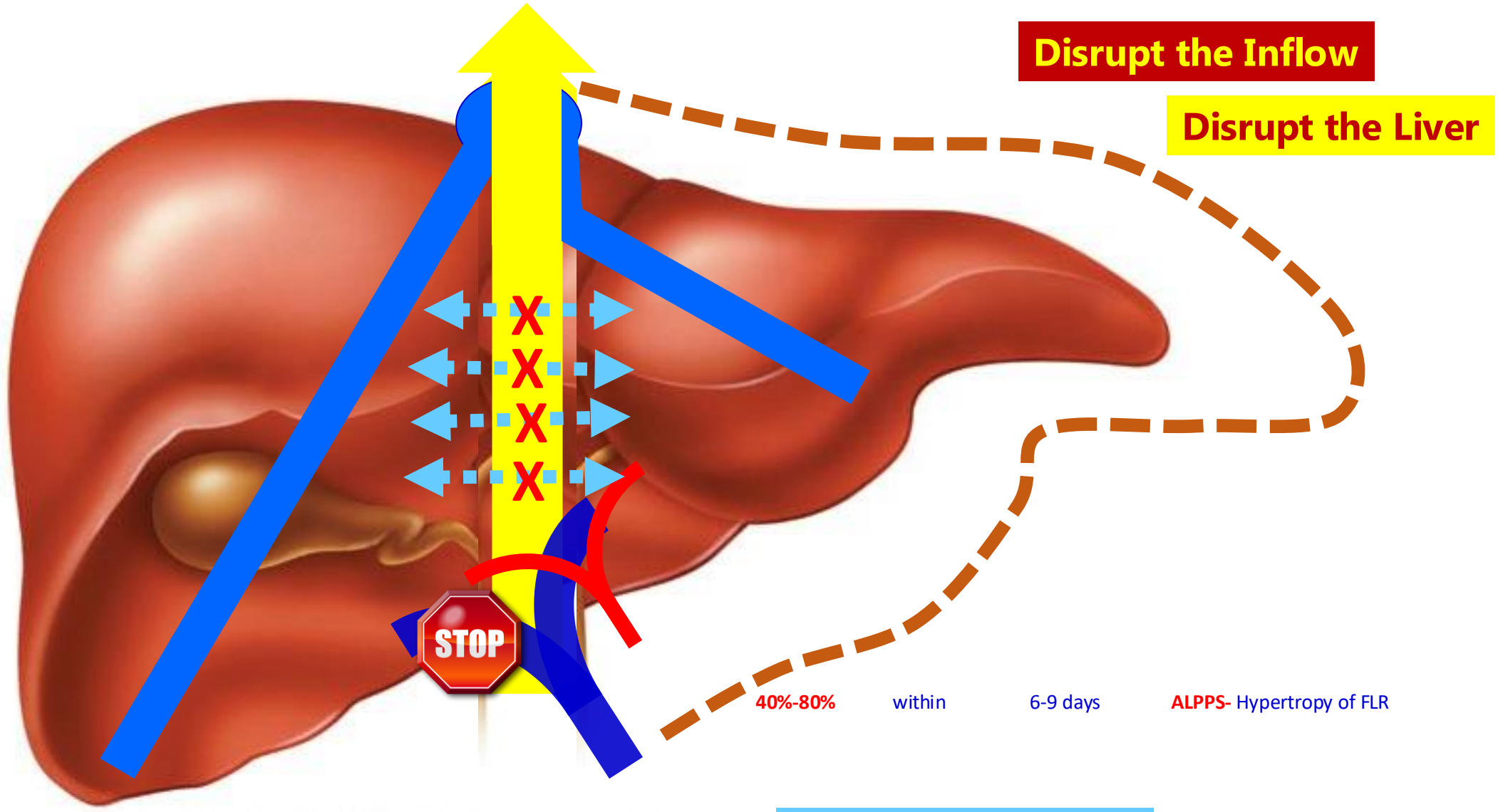
Schoellhammer HF, **Singh G**, Leong L. J Natl Compr Canc Netw. 2013 Sep;11 Suppl 4:S3-8. PMID:24158969

Designing Liver Resections: Creative Strategies of Inflow and Outflow disruption



ALPPS- Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy

Designing Liver Resections: Inflow disruption and Liver disruption → ALPPS

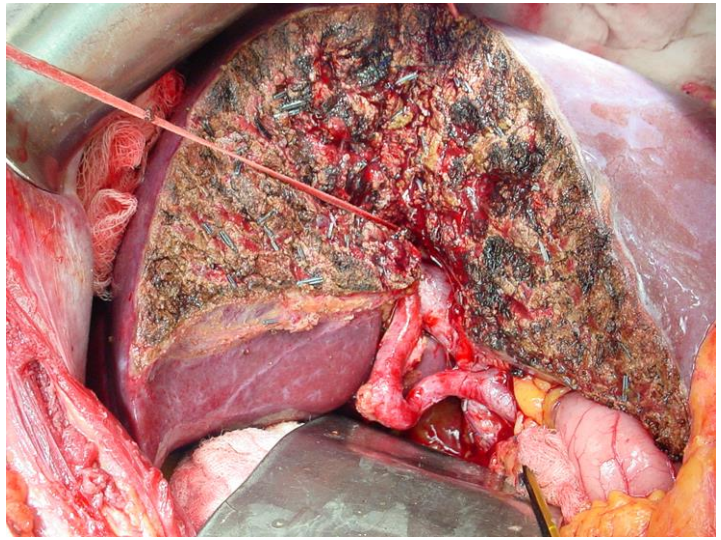


Cannot Disrupt the Artery!!

ALPPS- Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy

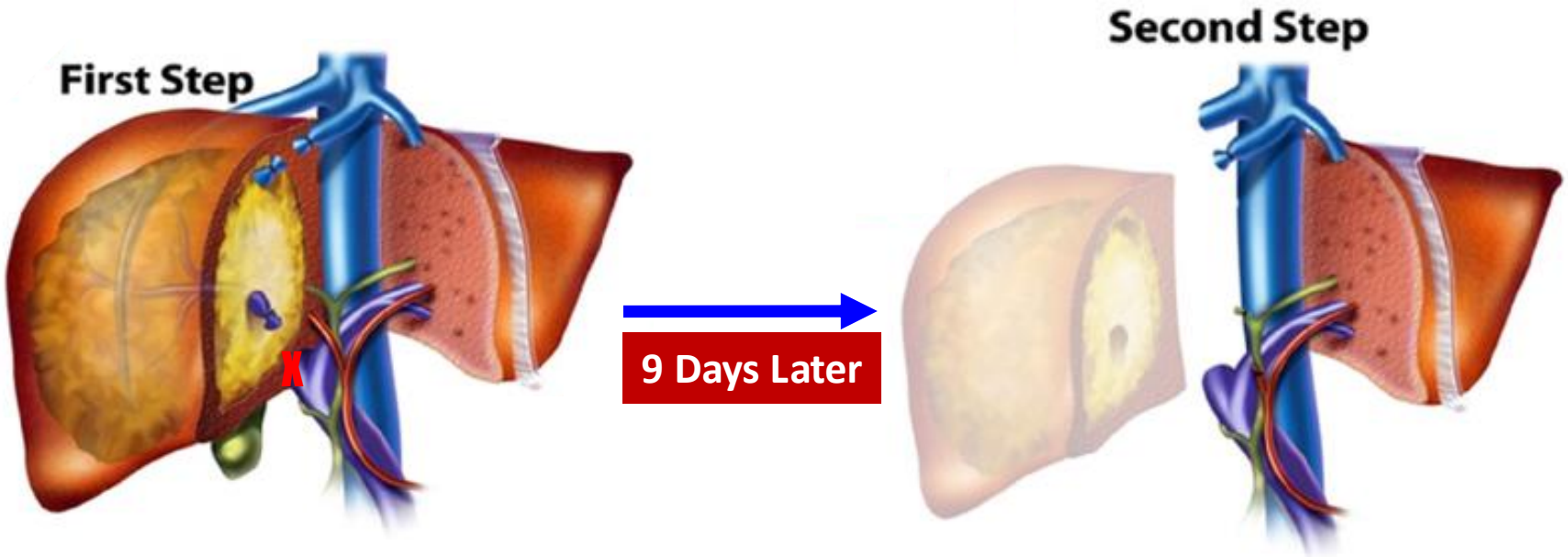
Strategy 5: ALPPS- Compensatory Hypertrophy

40%-80%	within	6-9 days	**ALPPS-** Hypertropy of FLR
8%-27%	within	2-60 days	**PVL/PVE**- Hypertropy of FLR



LVD supplant the role of ALPPS going forward. Metanalysis showed no difference between LVD and ALPPS in the hypertrophy of the FLR but significantly reduced morbidity and mortality with LVD.

Hepatobiliary Pancreat Dis. Int. 2023, 22, 221–227.

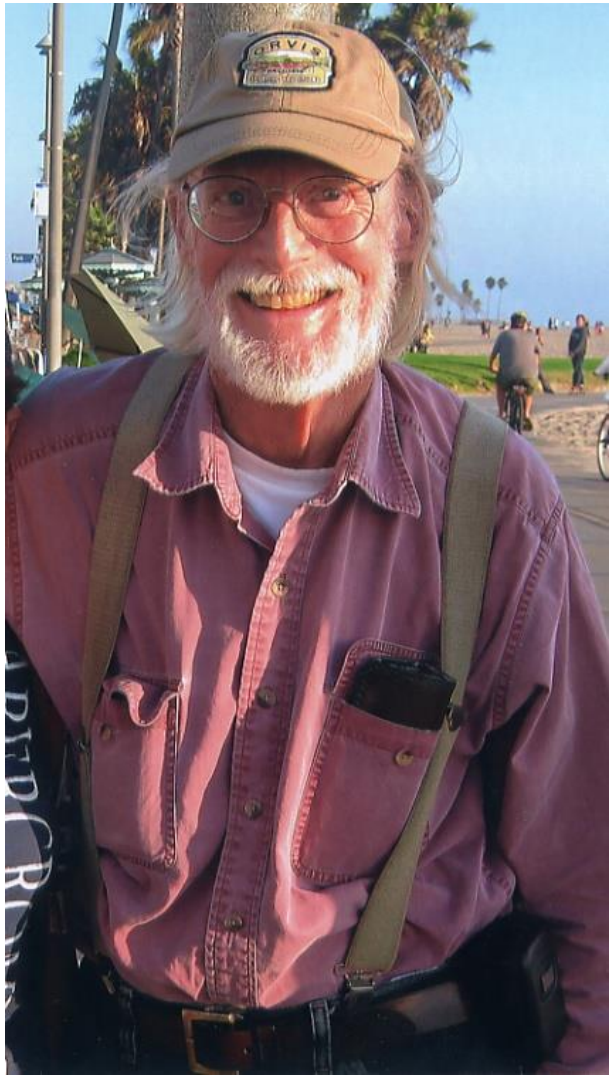


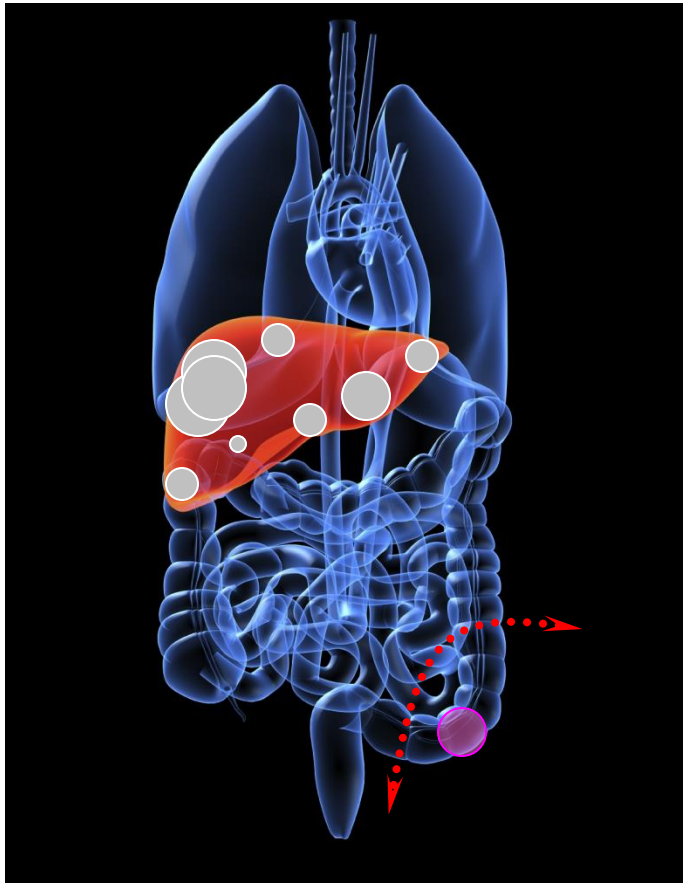
Operative morbidity	**16%-64%**
Mortality	**12%-23%** **down to 5% now**

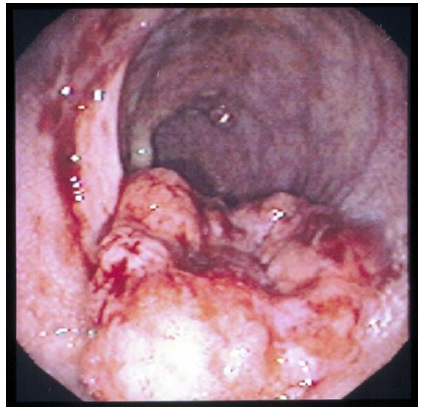
Ann Surg, 272 (2020), pp. 793-800

Increasing the size of the future liver remnant

Dec 13th, 2006

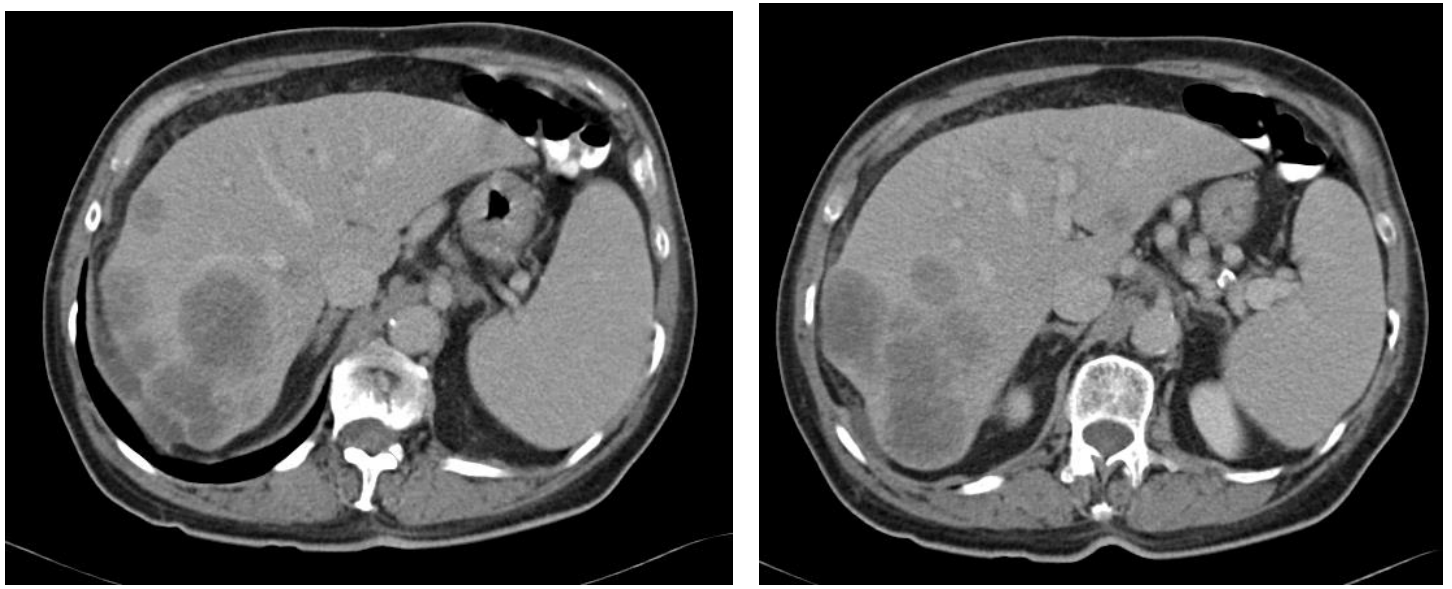


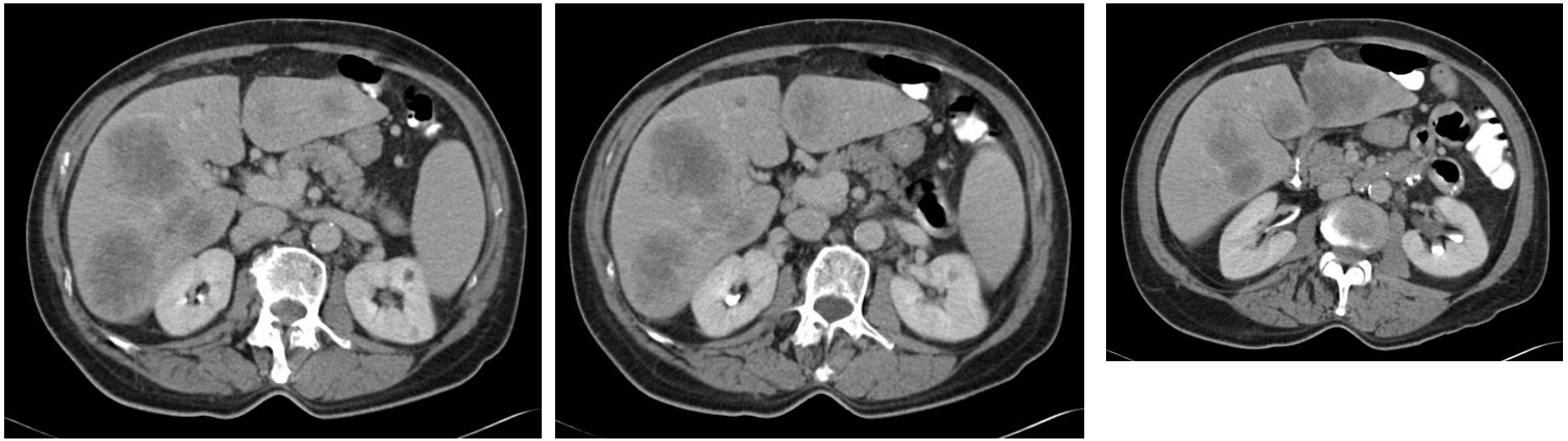




Case for PVE- CRLM

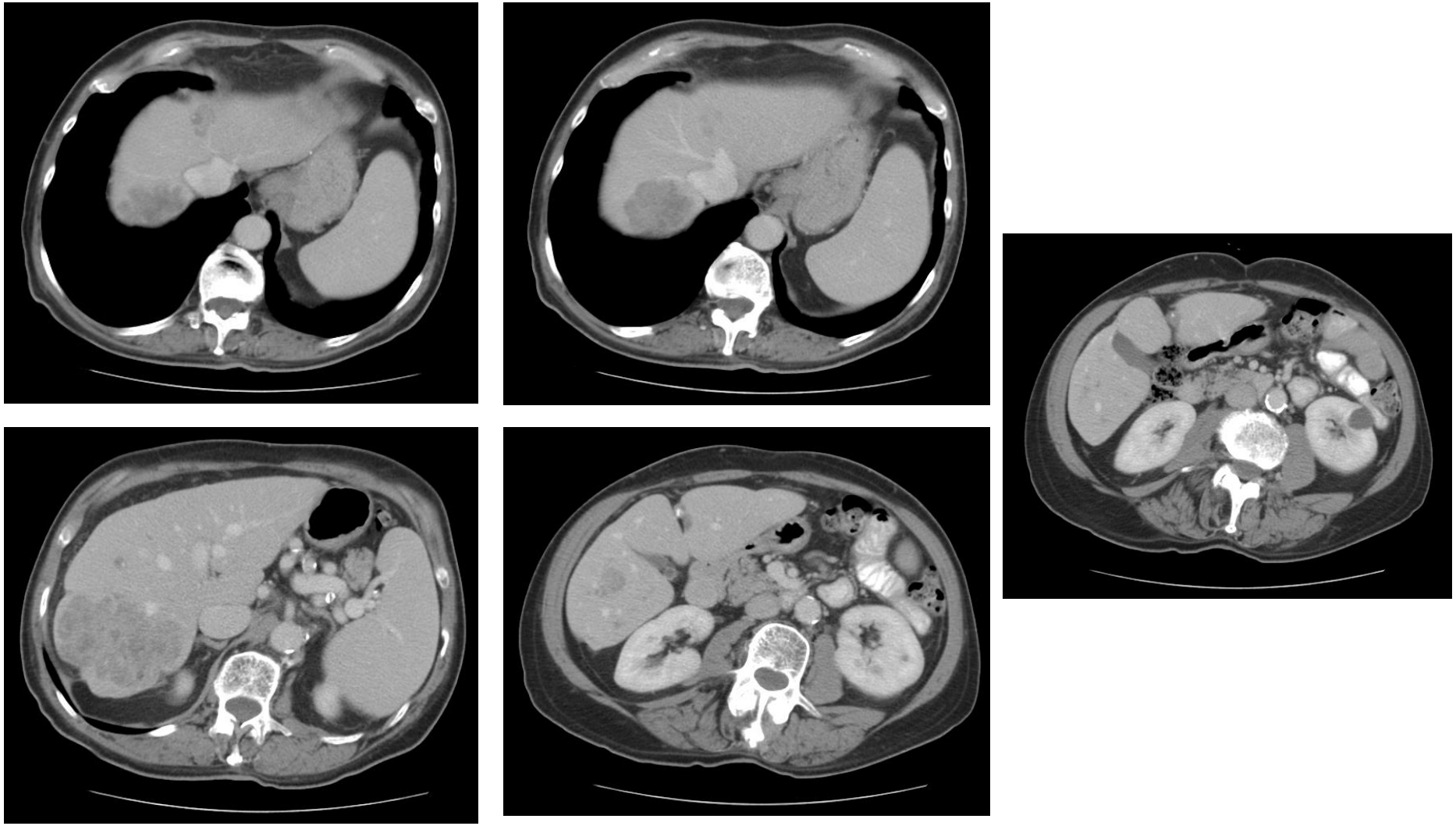
Dec 13th, 2006



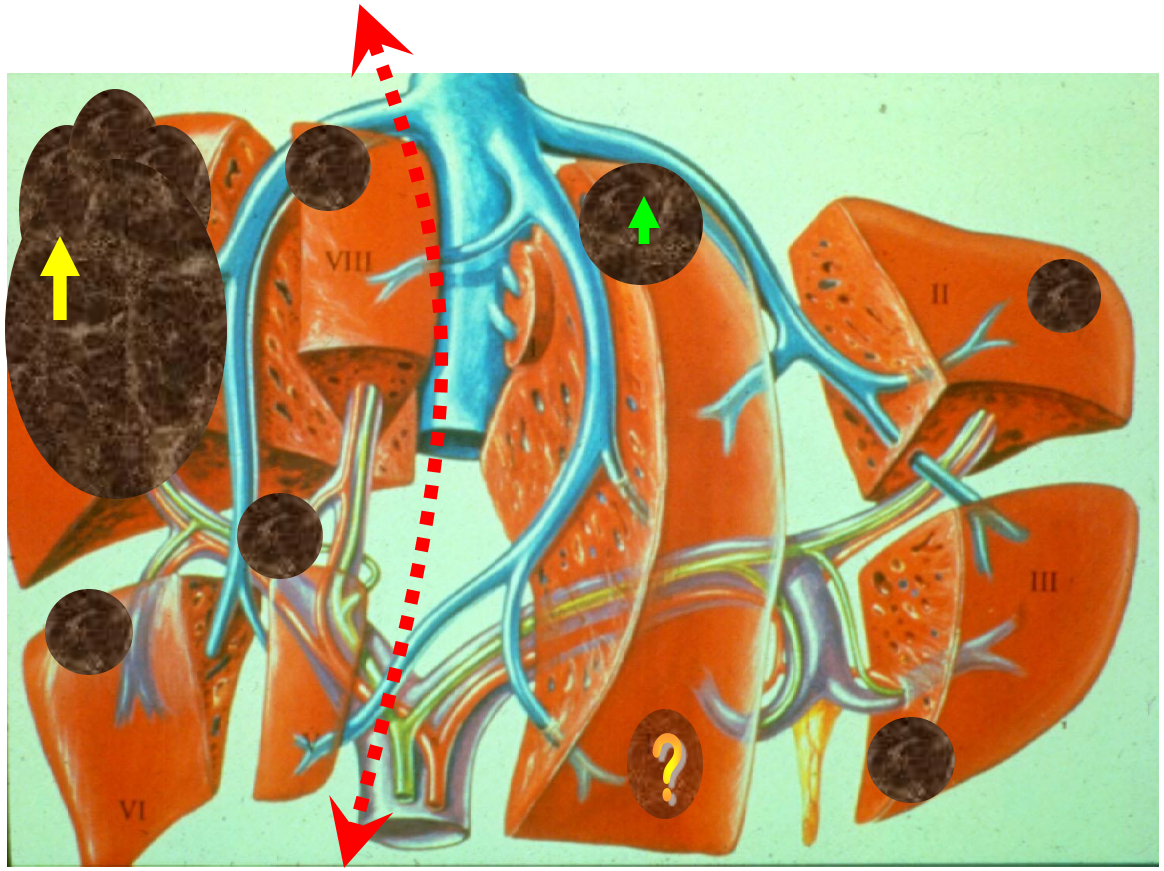


Excellent Response to Chemo →PVE

May 5th, 2009



Future liver remnant = 20-22% hence → PVE

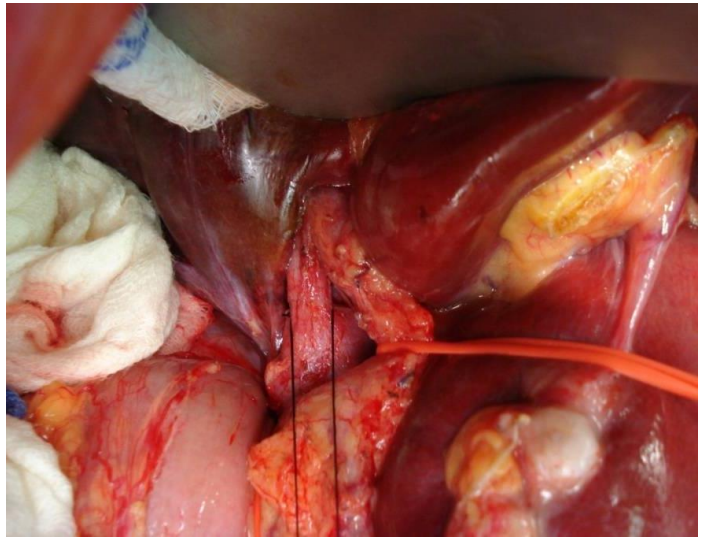


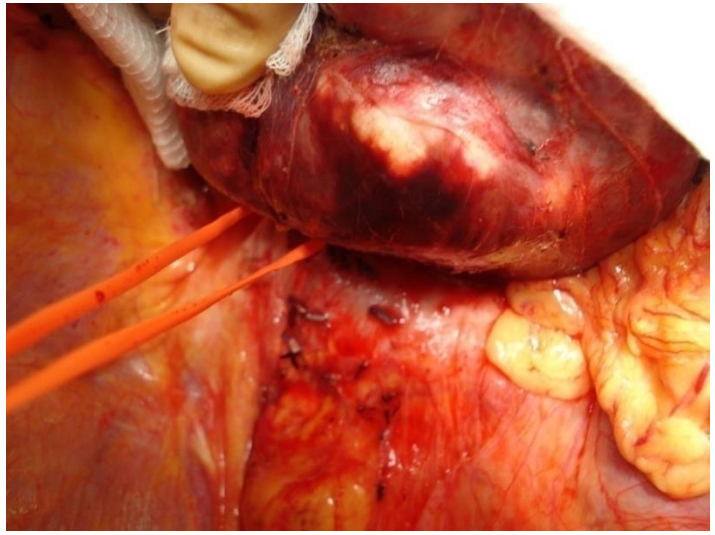
PLAN

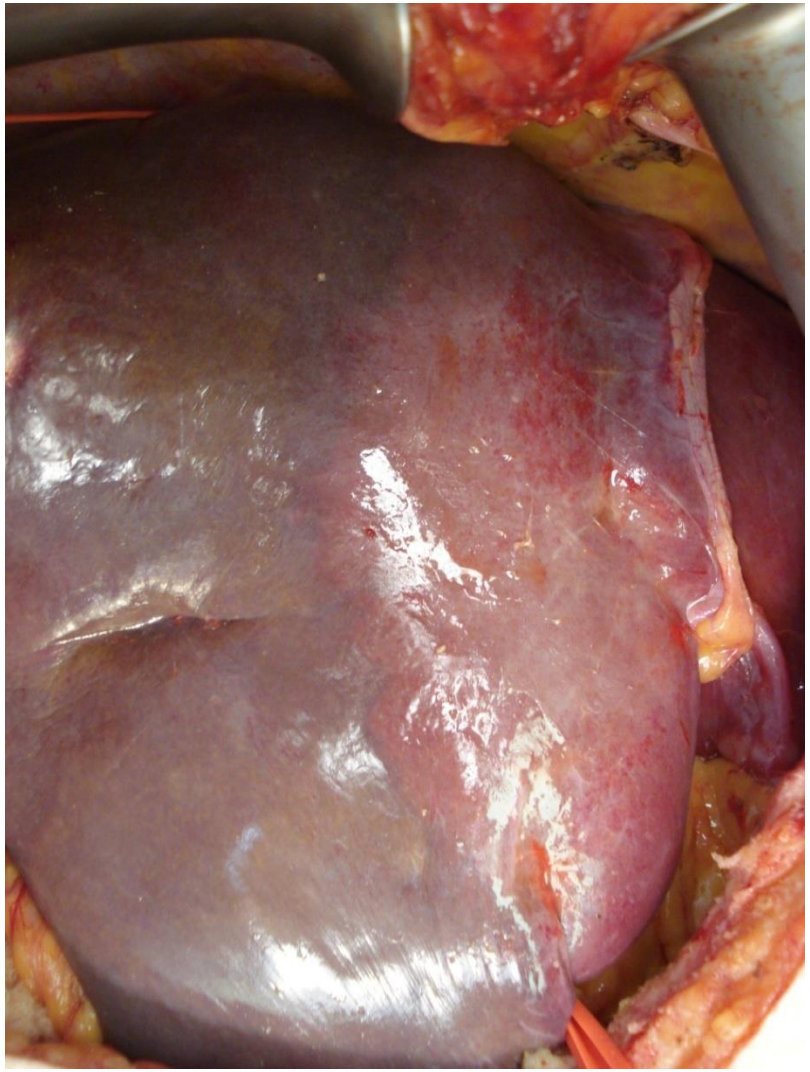
- Right Hepatectomy
- Wedge Segments 2, 3, 4
- Estimated Volume to be resected: **78-80%.** **FLR- 20-22%**

Case for PVE- CRLM

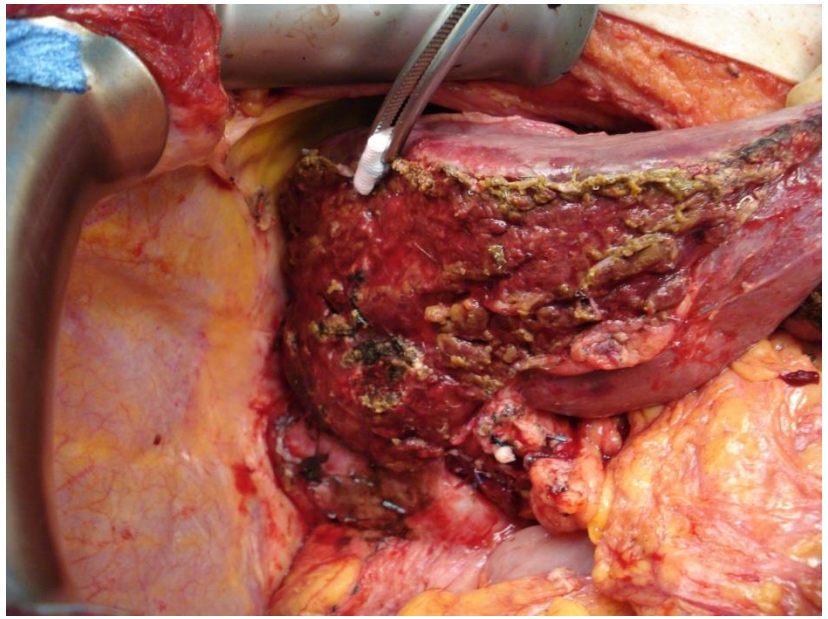
Case for PVE- CRLM

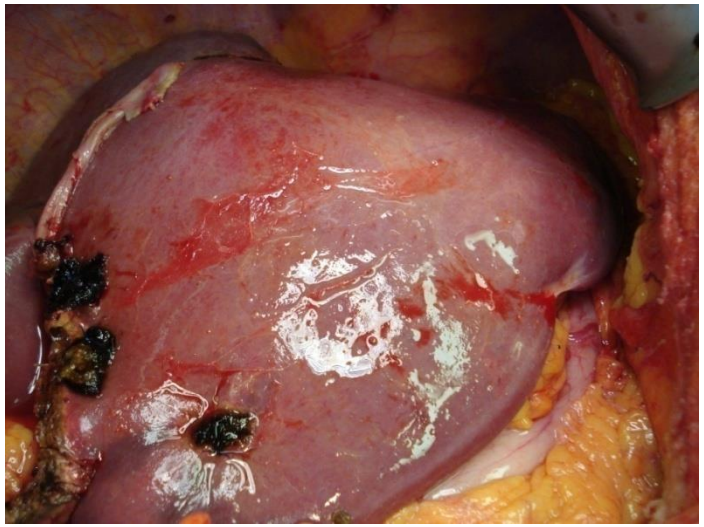


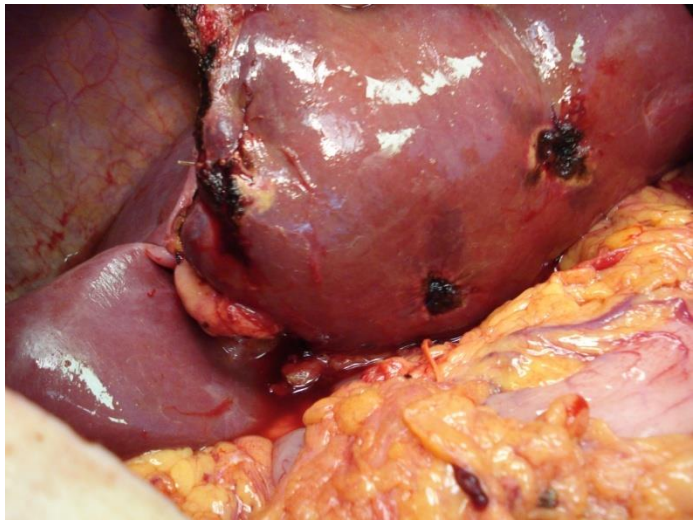




Case for PVE- CRLM



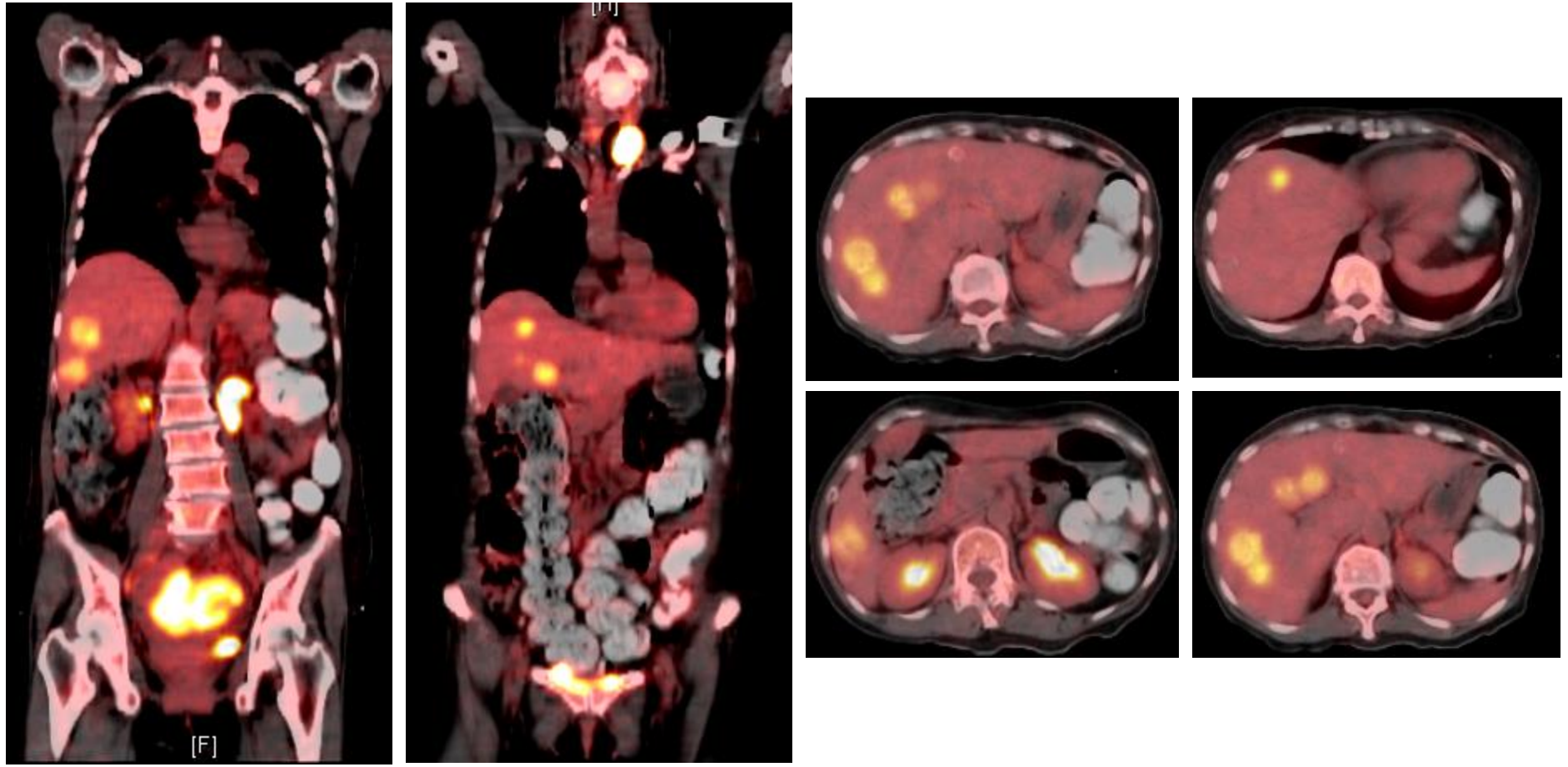




Staged Hepatectomies- CRLM

LG

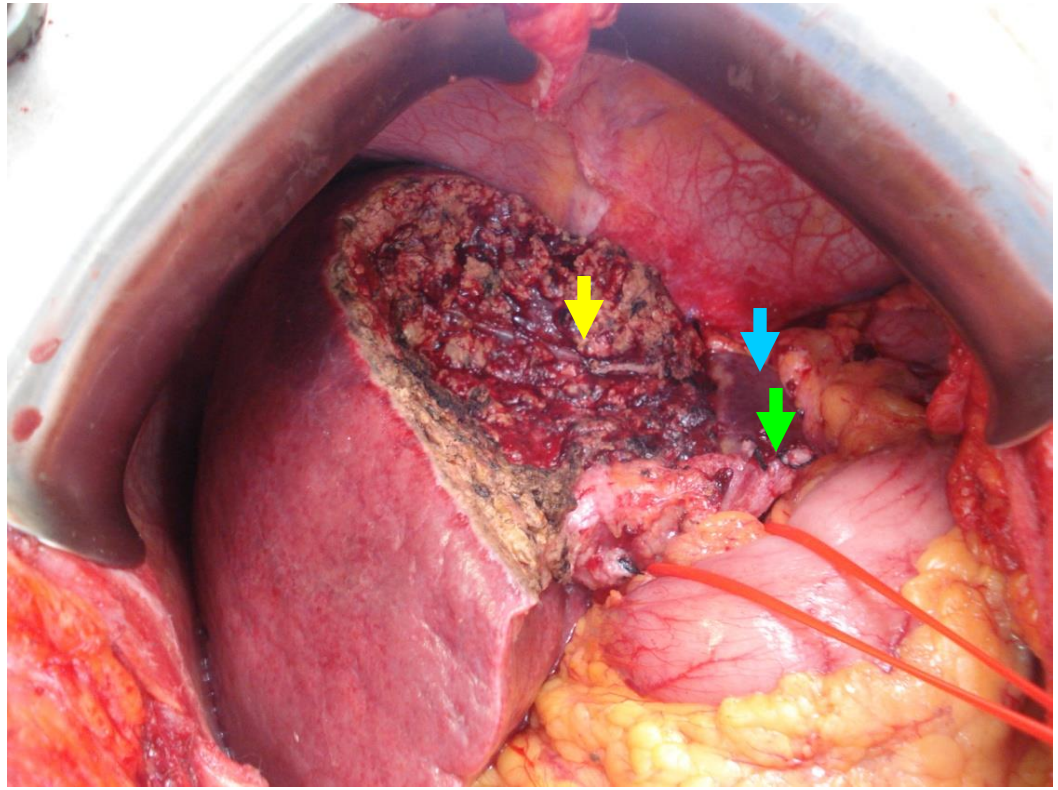
Mar 5th 2010

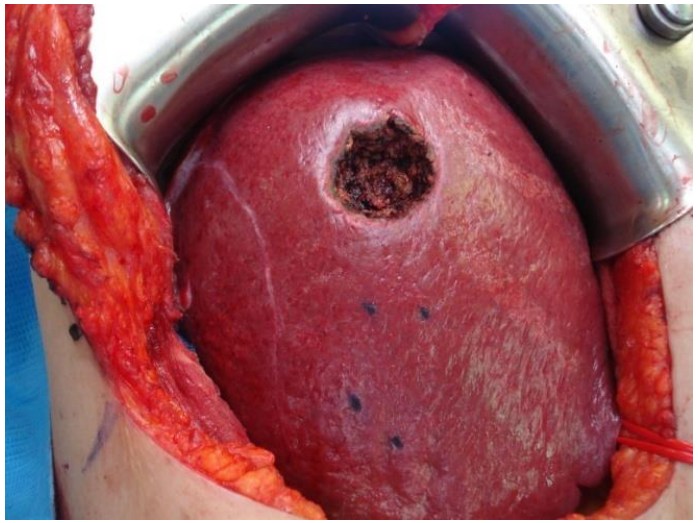


Stage 1: Left Hepatectomy + Right Wedges

LG

Jan 11th 2011

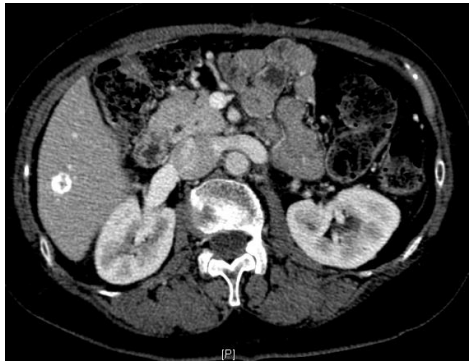




Stage 2: Hepatectomy- Seg VI Resection

LG

May 5th 2011

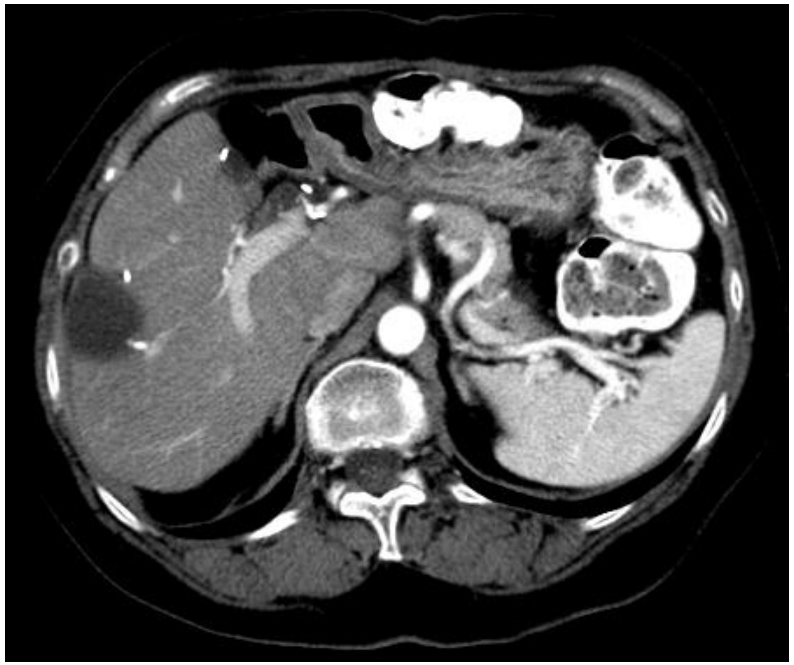


Liver Metastases- CRLM

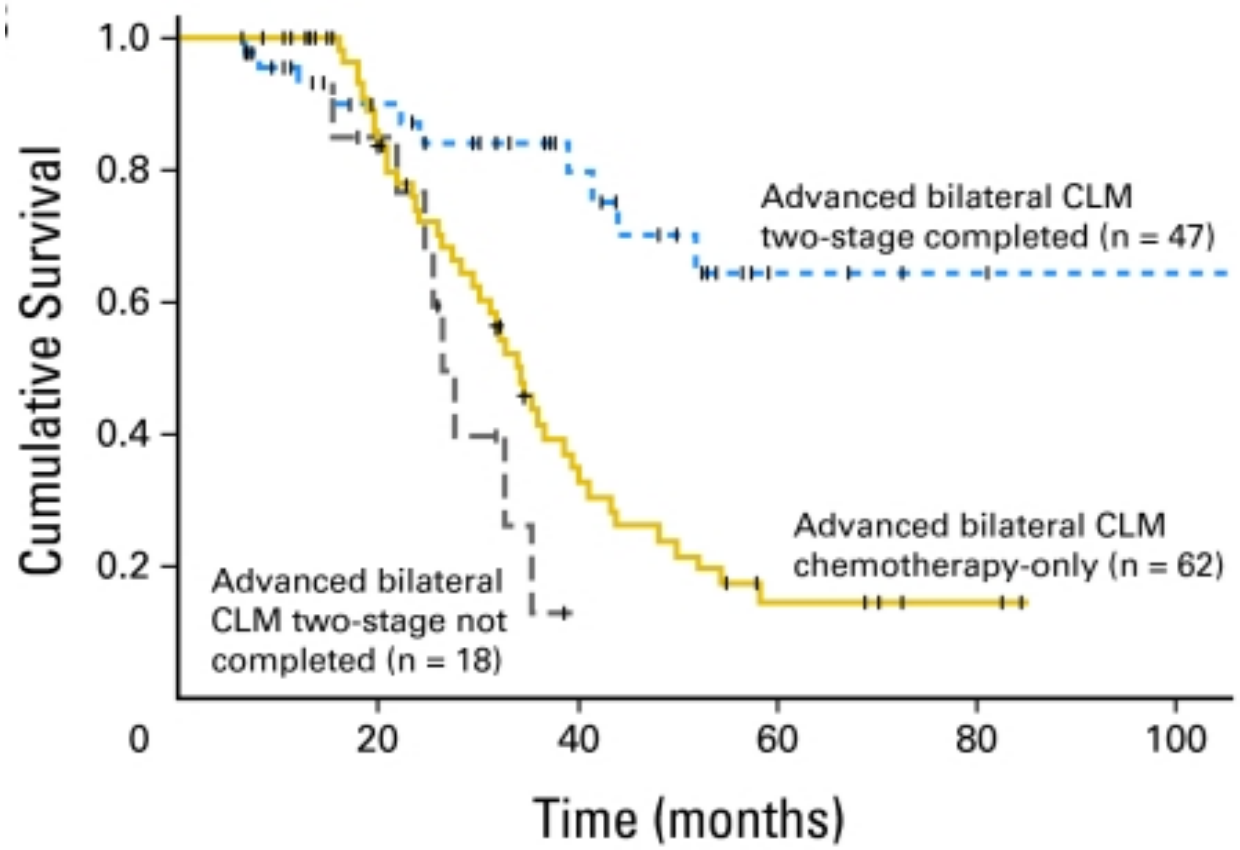
LG

Feb 12th 2015

Approx: 4.5 year



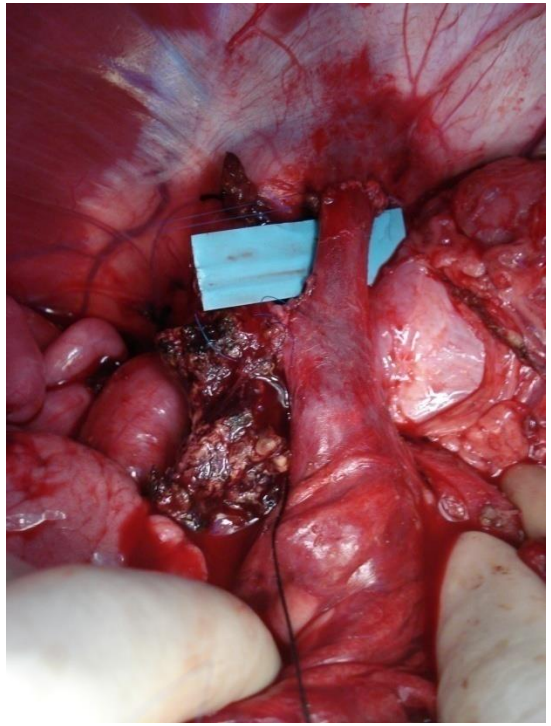
Bilateral Colorectal Liver Mets

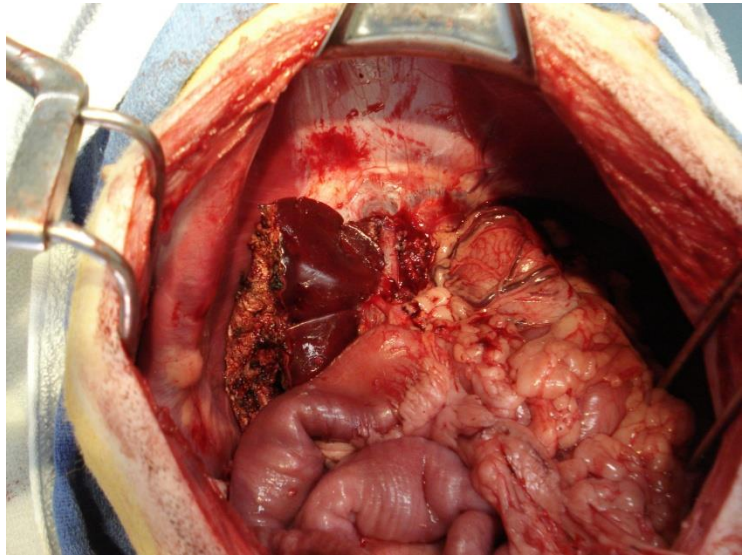


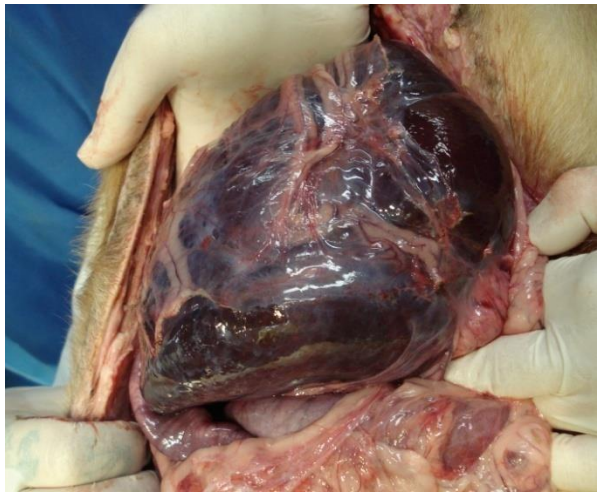
MD Anderson: J Clin Oncol. 2011;**29**:1083–1090

Pushing the limits- 90% Liver Resection

Strategy 6: Portahepatic Shunt



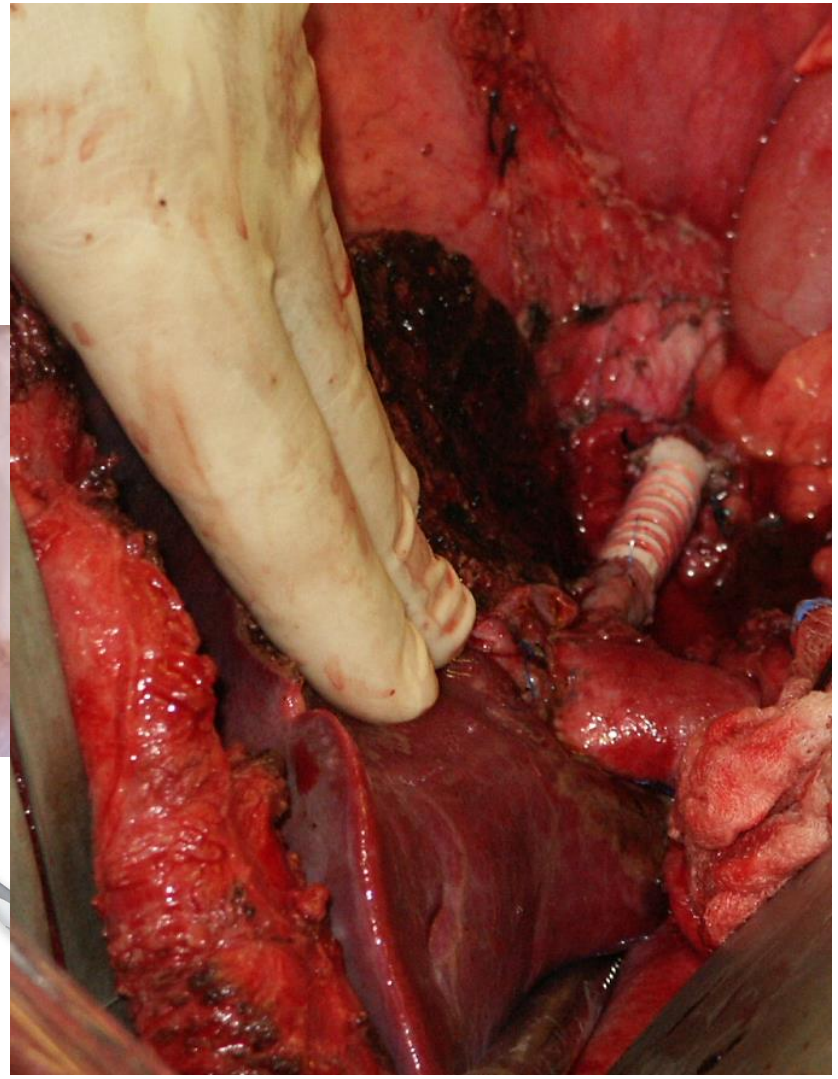


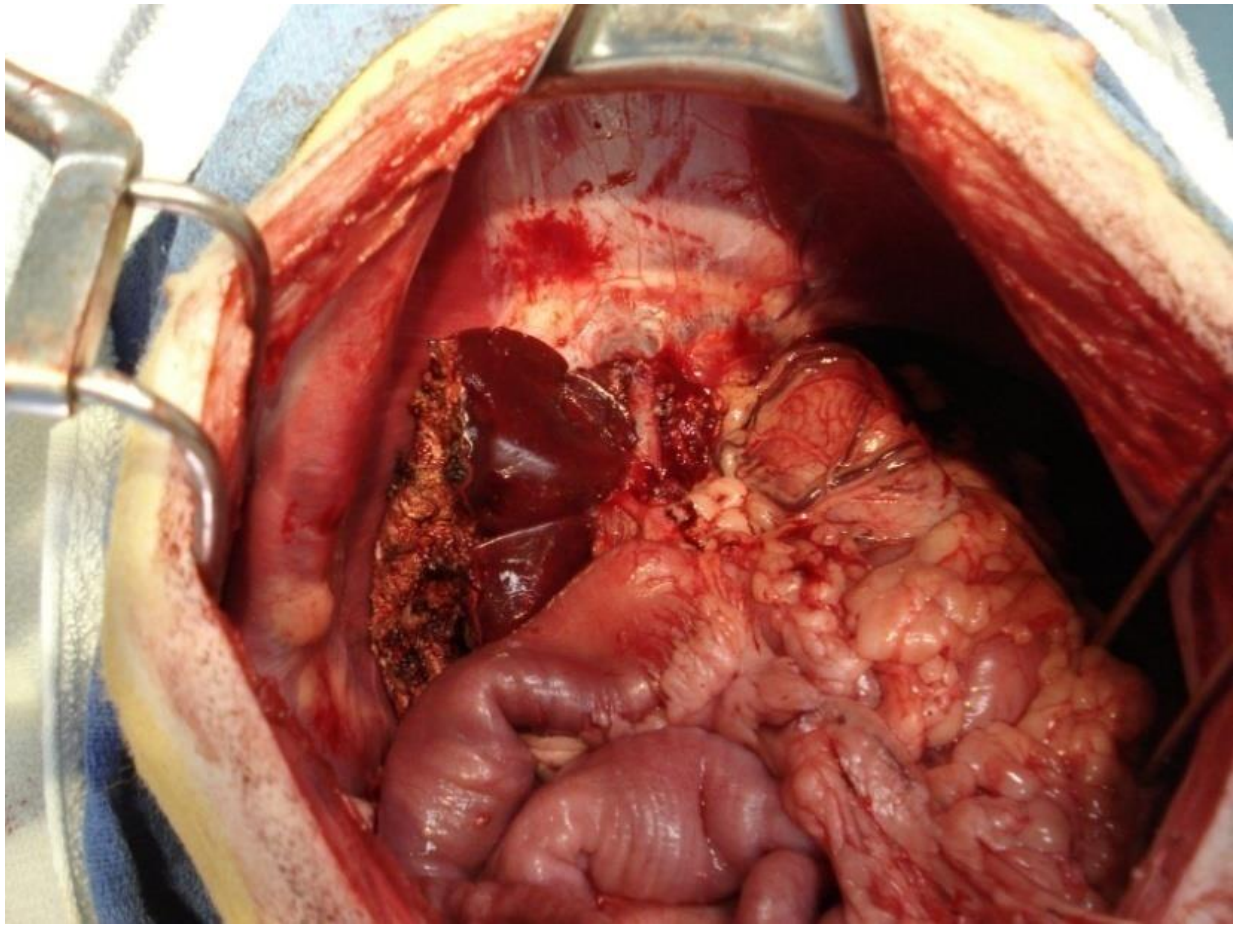


S Steen, C Conway H Kargozaran, **S Gagandeep**. Development of a Clinically Relevant Canine Model for 90% Extended Hepatectomy. ***ILAR J 52(4). 2012***

Pushing the limits- 90% Liver Resection

Strategy 6: Portahepatic Shunt

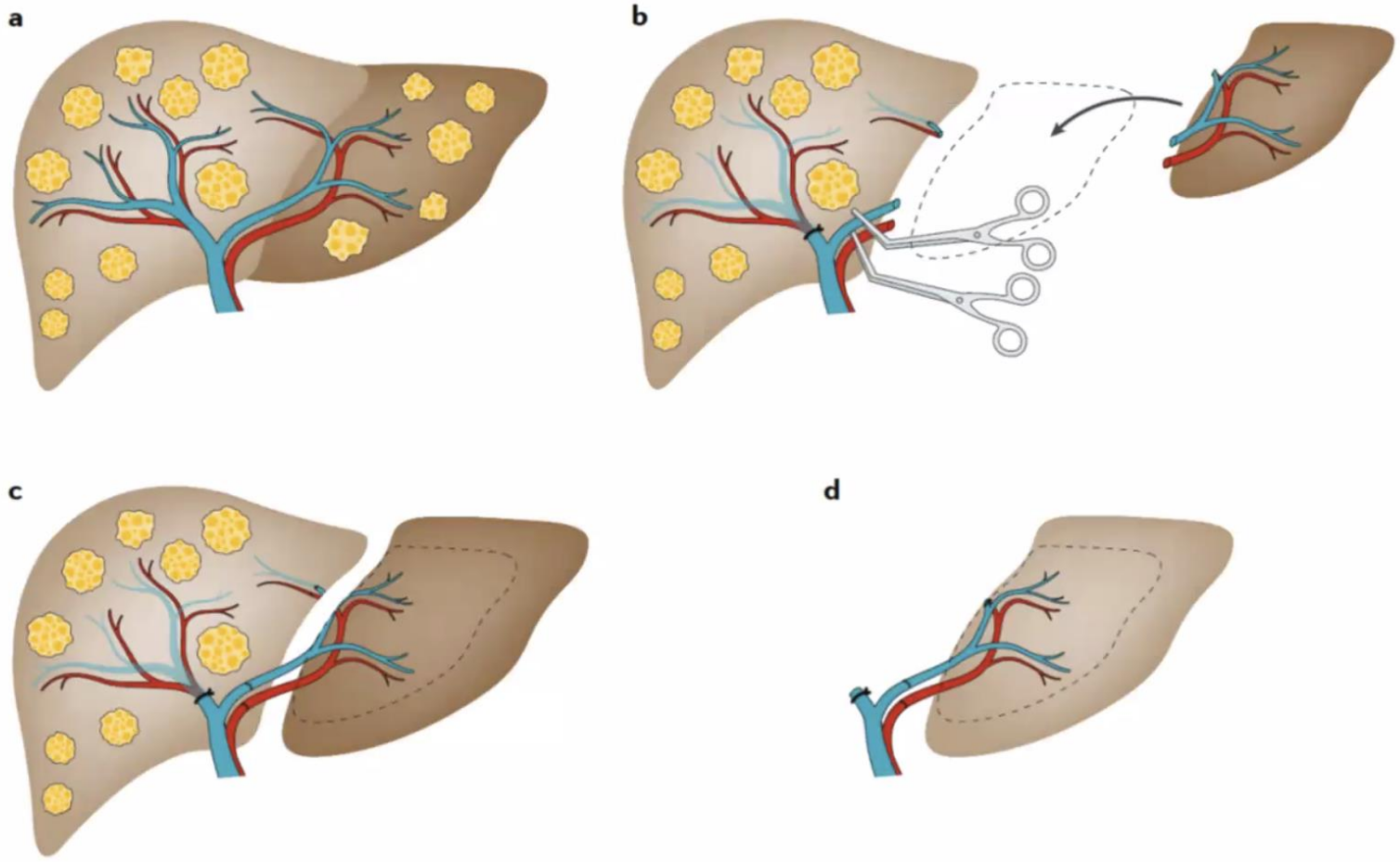




S Steen, WC Conway, H Kargozaran, **S Gagandeep**. 90% Extended Hepatectomy with Portahepatic Shunt in a Canine Model- A Feasibility Study. *ILAR J 52(4). 2012*

RAPID- Resection and Partial Liver Transplant (Seg 2 & 3) with Delayed Total Hepatectomy

Strategy 7: Partial Liver Transplant



Transplant a small auxiliary left lateral liver graft (segment 2+3) and ligation of the right portal vein, followed by hepatectomy of the native liver at a second stage after sufficient regeneration of the graft

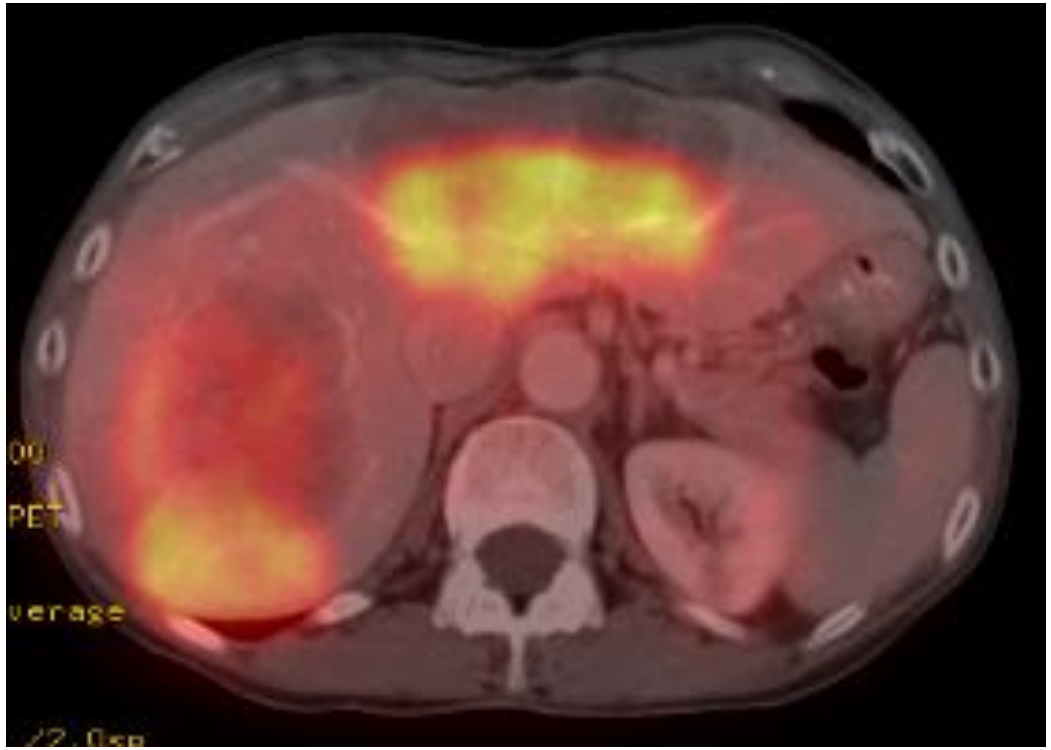
RAPID concept: Ann Surg, 262 (2015), pp. e5-e9

Liver Metastases- CRLM- Our Evolving Concept

Strategy 8: One stage resection + IRE

1003-1383

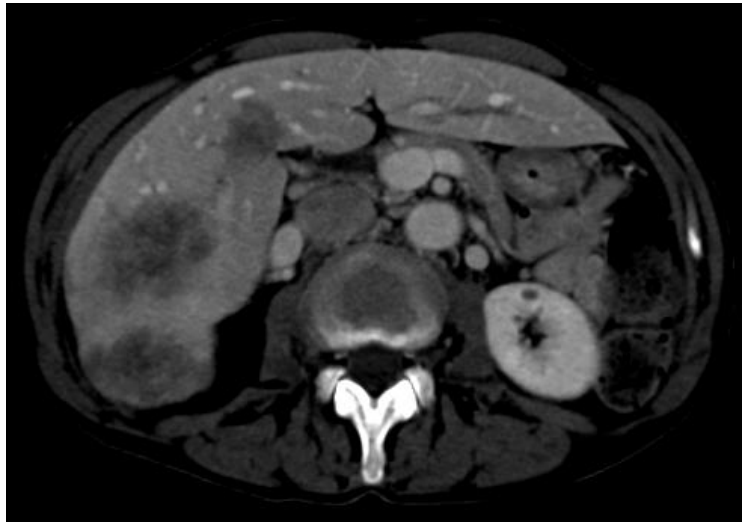
Feb 21st 2012



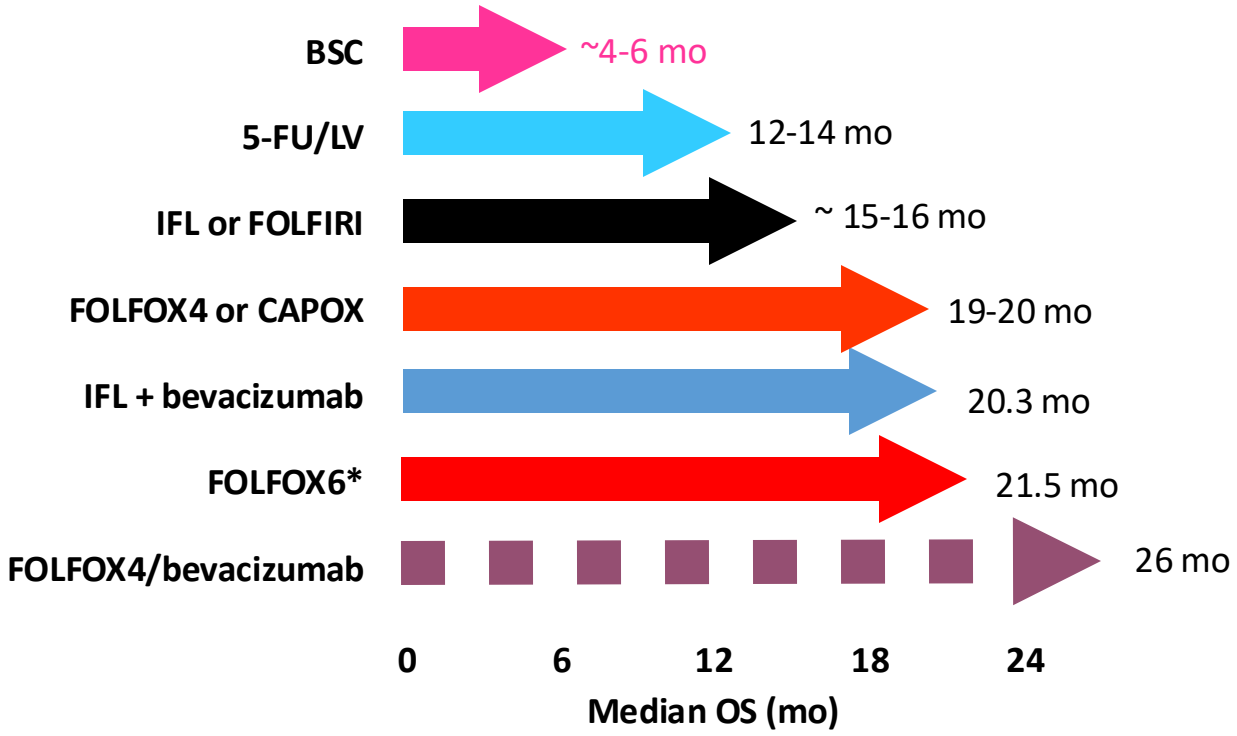
Liver Metastases- Can we make it all 1 Stage Surgery?

SS

Feb 21st 2012



A changing landscape:
Improving survival in pts with mCRC

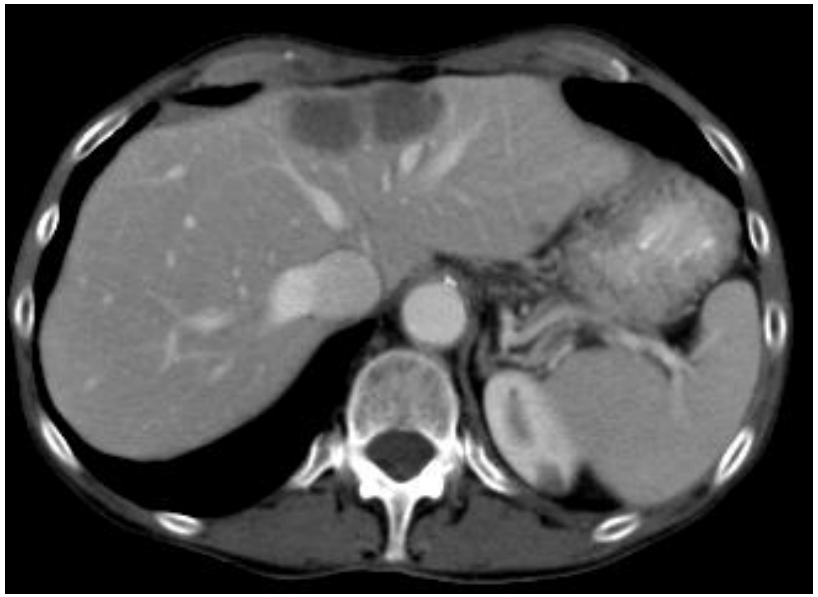


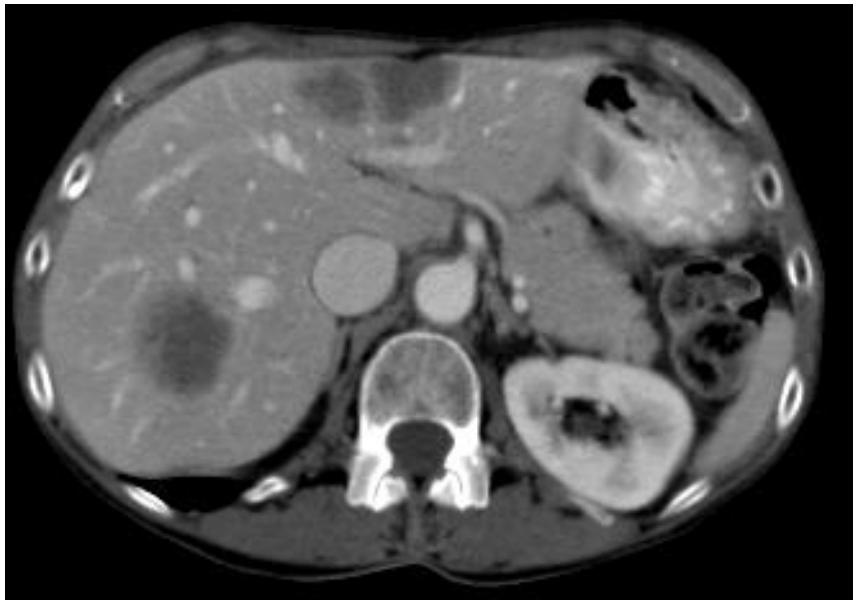
FOLFOXIRI, Erbitux, Cetuximab, Regorafenib etc. etc.

Liver Metastases- Can we make it all 1 Stage Surgery?

1003-1383

Apr 13th 2012

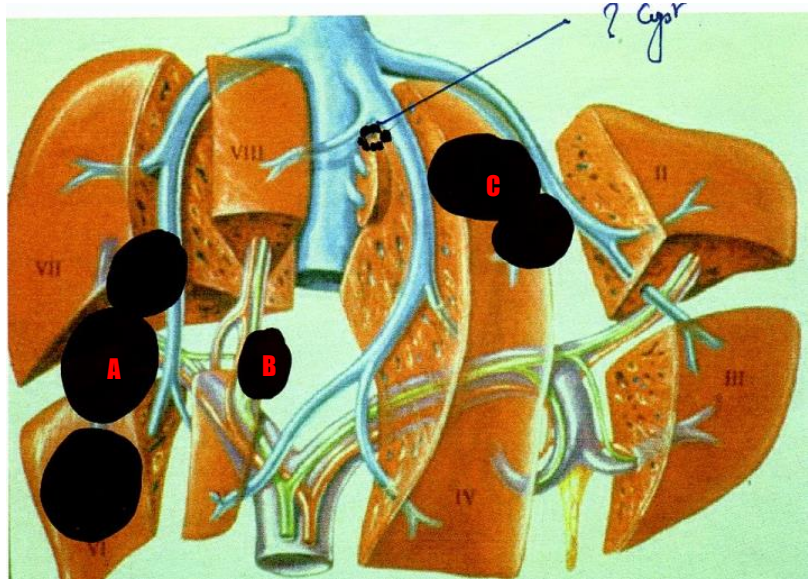


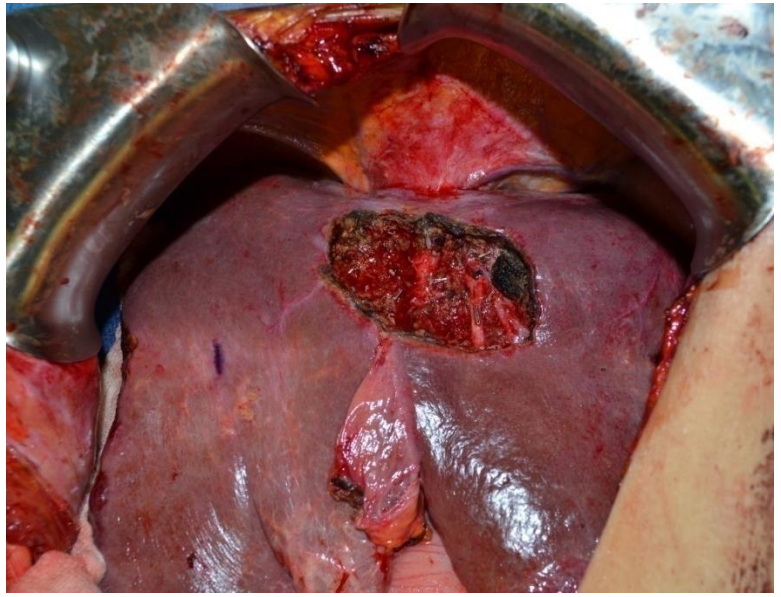


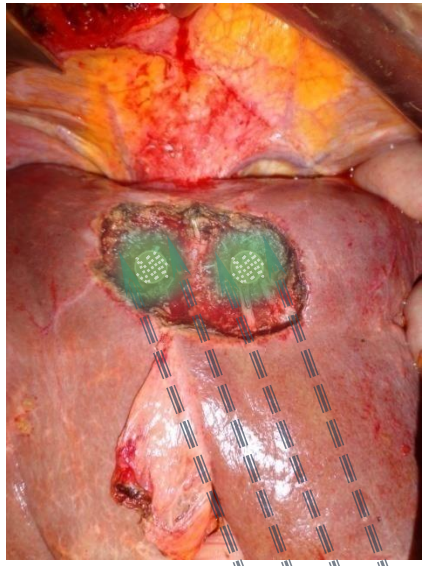
CRLM- Resection + Nanoknife→ Making it all 1 Stage Surgery

SS

June 28th 2012







Surgery : discharged POD 8

Right Hemicolectomy
A: Right Posterior Sectionectomy (Seg 6 & 7)
B: Wedge Resection of Seg 4B/ 5 lesion…..sitting right on the portal vein.
So basically enucleated…..no attempt at getting margins
C: Wedge Resection of lesions in Seg 2 and 4A.
No attempt at getting margins….as this was sitting on the bifurcation of the left hepatic vein. Bed Nanoknifed (Irreversible Electroporation). Grossly all tumor removed.

Excellent Liver Hypertrophy- Following 1 Stage Surgery

SS

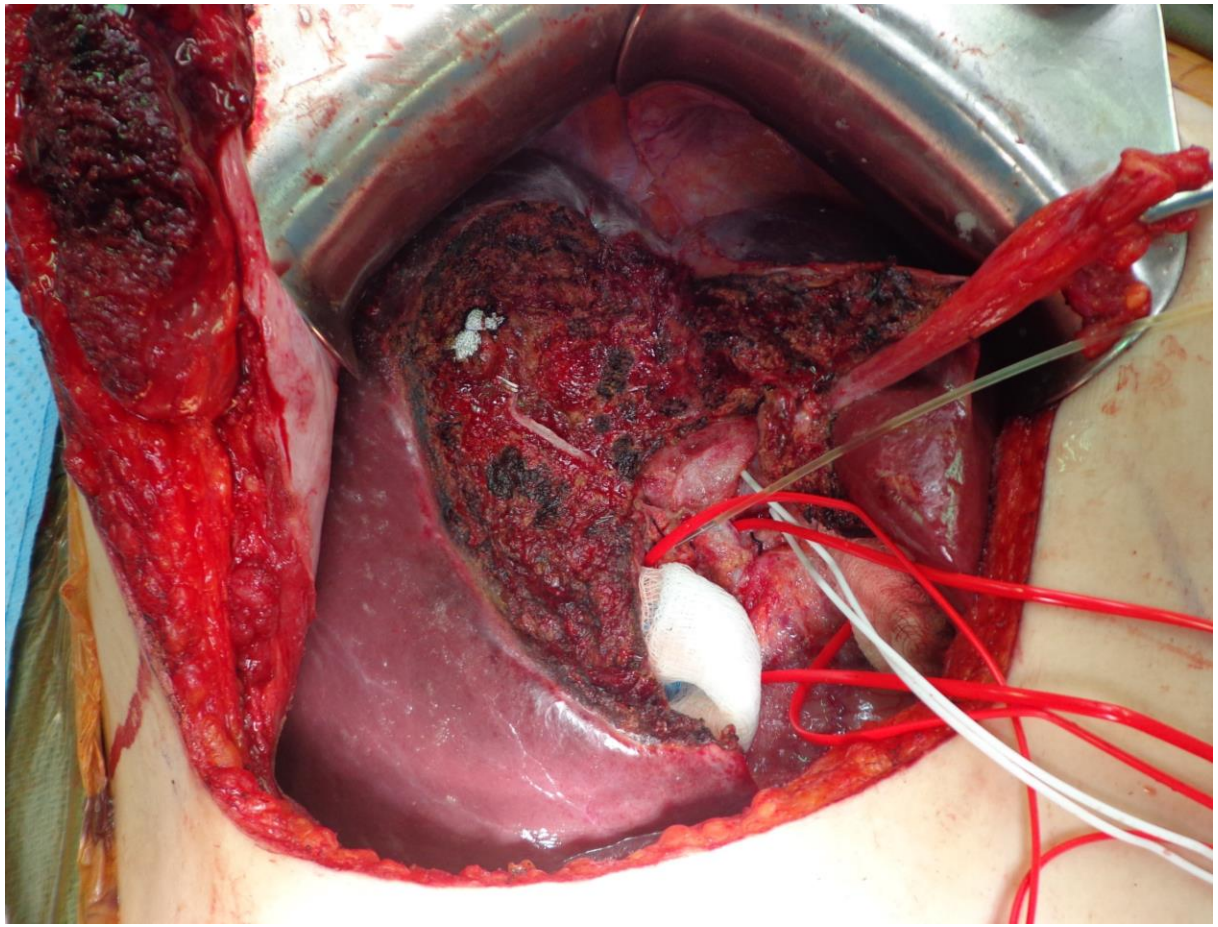
Mar 19th 2019

Schoellhammer HF,...., **Gagandeep S**. BMC Cancer 2015, 15:271.

Oligometastatic CRLM- Work with your oncologist till you get the desired response?

10/22/12

02/22/13



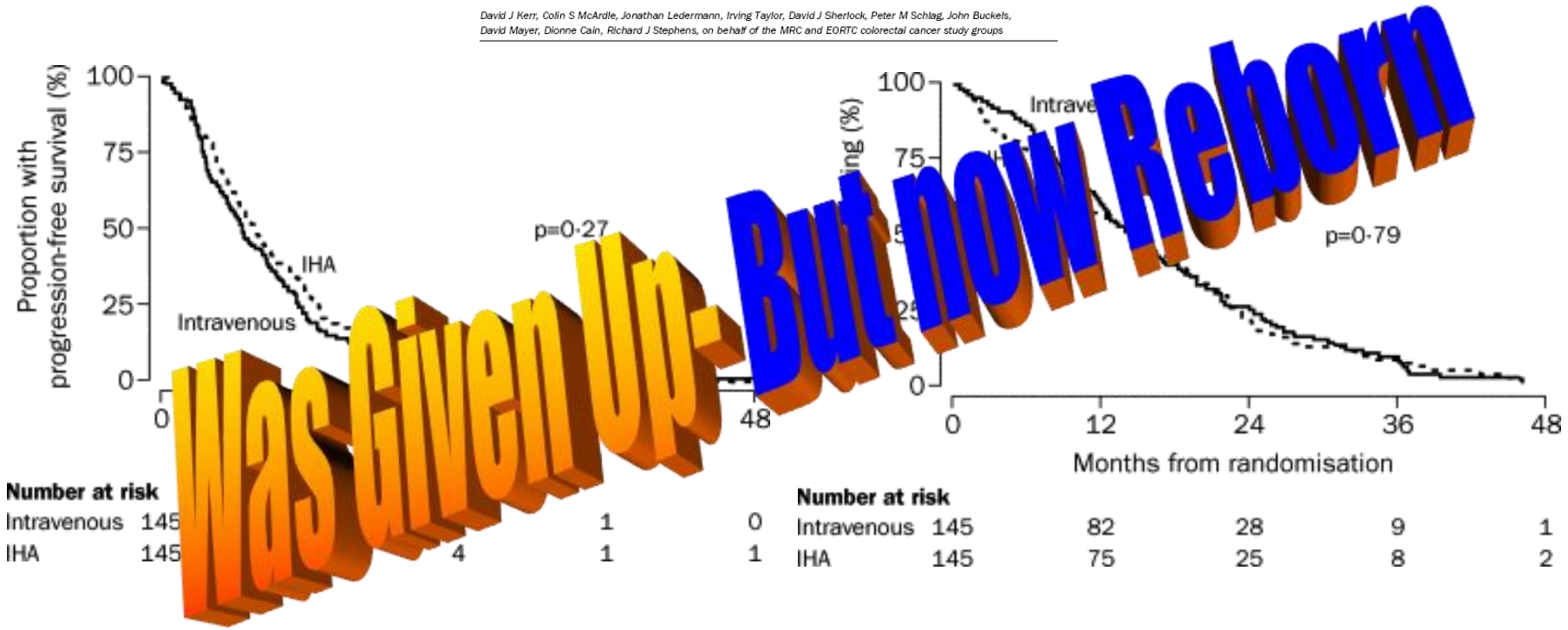
Hepatic Artery Infusion

HAI = Systemic Chemo (1994-2001)

ARTICLES

Intrahepatic arterial versus intravenous fluorouracil and folinic acid for colorectal cancer liver metastases: a multicentre randomised trial

David J Kerr, Colin S McArdle, Jonathan Ledermann, Irving Taylor, David J Sherlock, Peter M Schlag, John Buckels, David Mayer, Dionne Cain, Richard J Stephens, on behalf of the MRC and EORTC colorectal cancer study groups



Was Given Up- But now Reborn

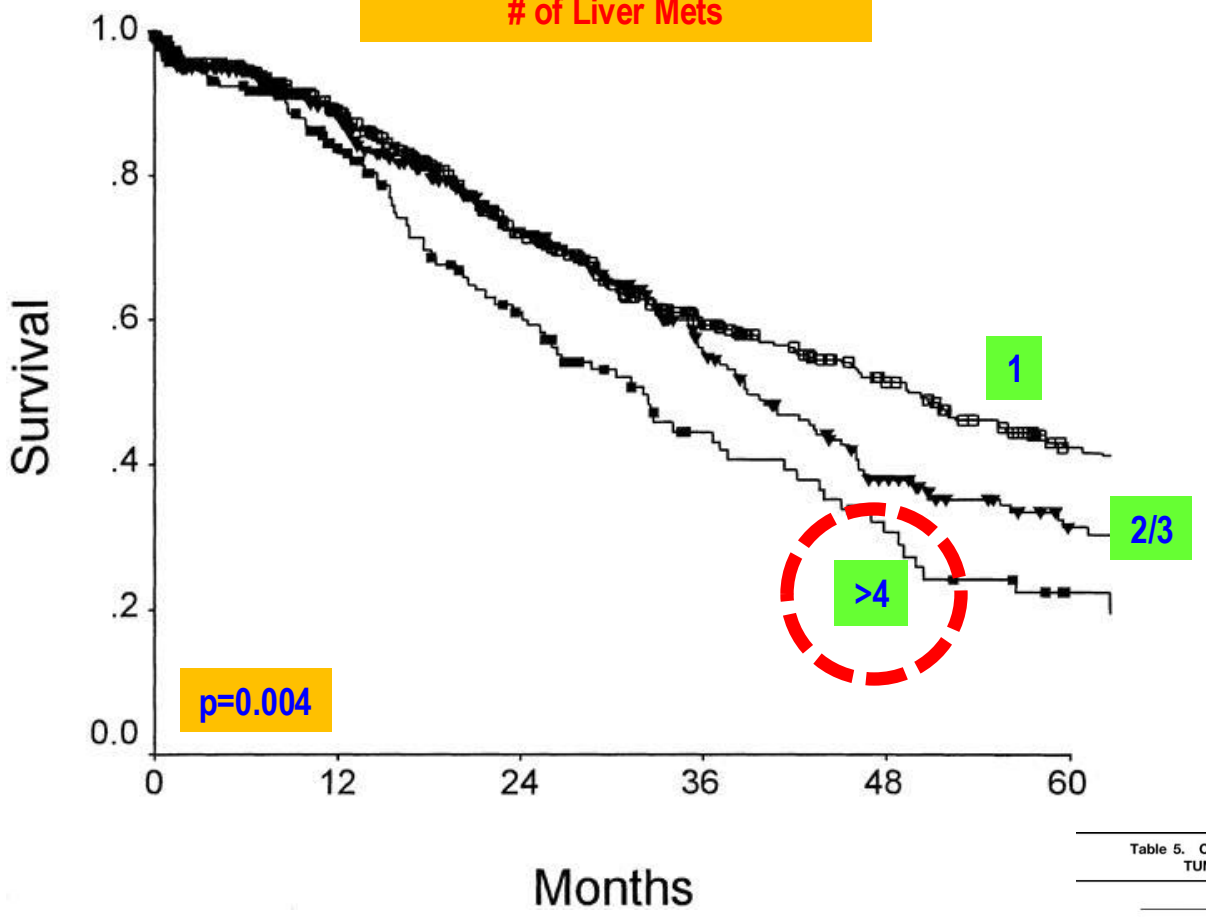
Results showed no evidence of an advantage in progression-free survival or overall survival for the IHA group; Thus continued use of this regimen cannot be recommended outside of a clinical trial

THE LANCET

Volume 361, Issue 9355 , 1 February 2003, Pages 358-359

Clinical Risk Score for CRLM

1 Point for Each: Node-positive primary; DFI <12m; >1 tumor; Size > 5cm; CEA >200



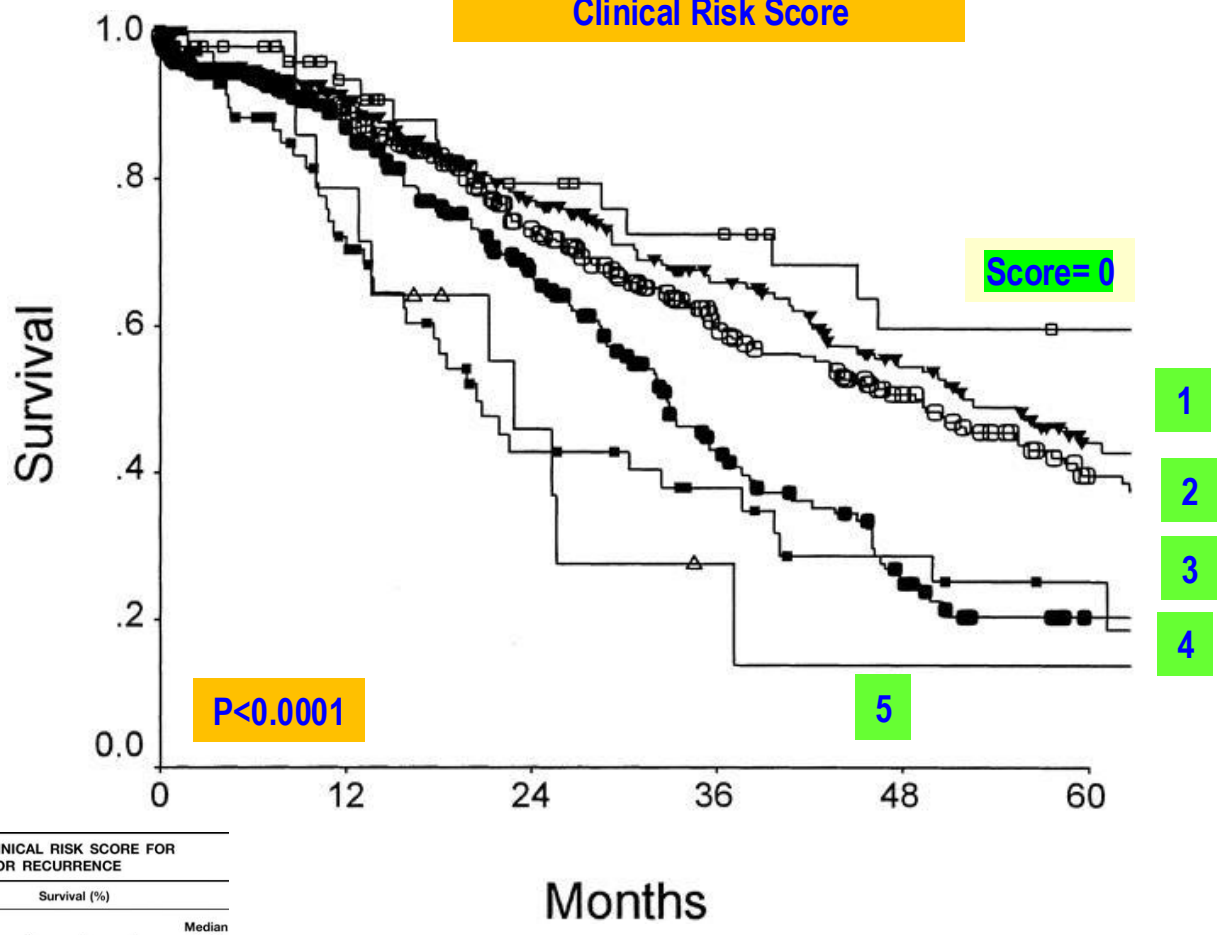


Table 5. CLINICAL RISK SCORE FOR TUMOR RECURRENCE

	Survival (%)					
Score	1-yr	2-yr	3-yr	4-yr	5-yr	Median (mo)
0	93	79	72	60	60	74
1	91	76	66	54	44	51
2	89	73	60	51	40	47
3	86	67	42	25	20	33
4	70	45	38	29	25	20
5	71	45	27	14	14	22

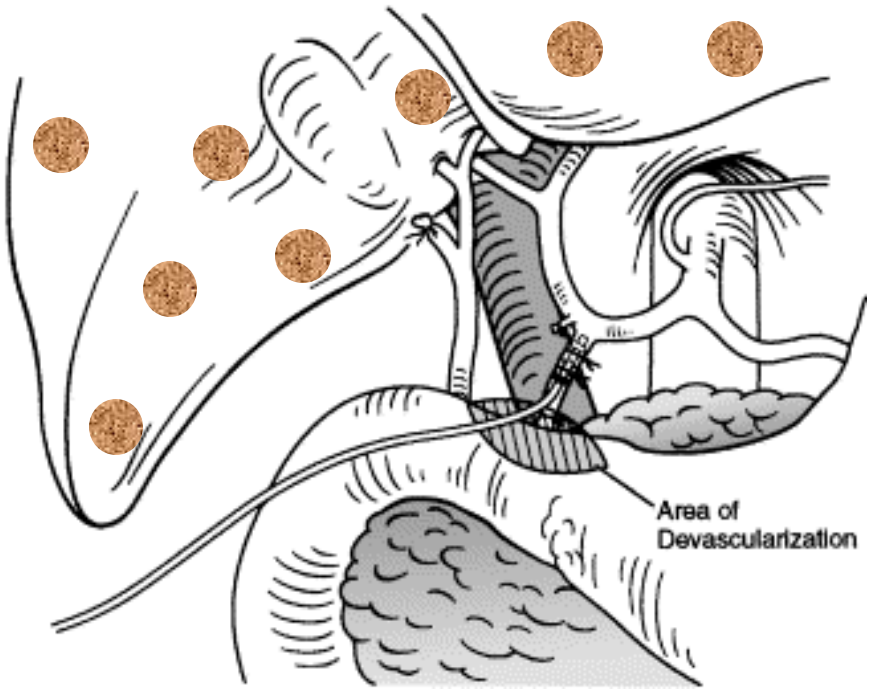
Ann Surg. 1999 Sep; 230(3): 309.

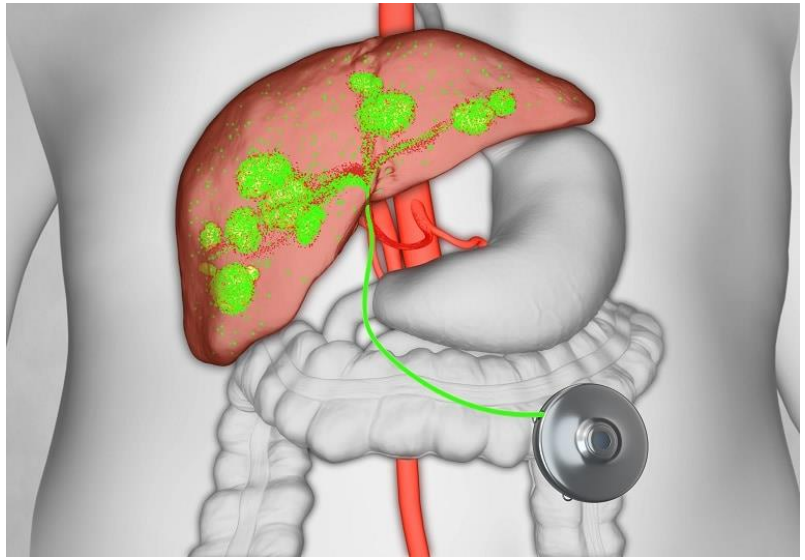
Designing Liver Resections

Strategy 9: Hepatic Artery Infusion Pumps

HAI

- Better response rate for multiple colorectal liver mets





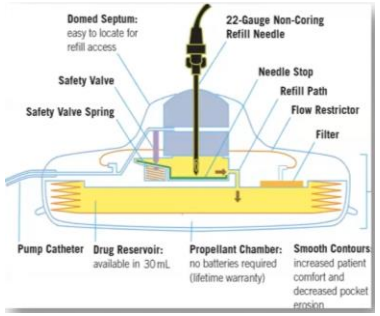
HAr→ Tumors >2-3 mm

PVn → Hepatic Parenchyma

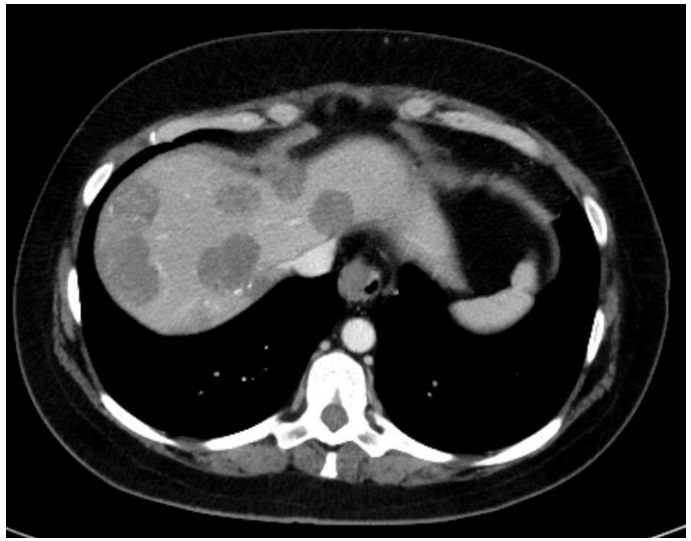
FUDR → 95-99% Extraction- 1st pass

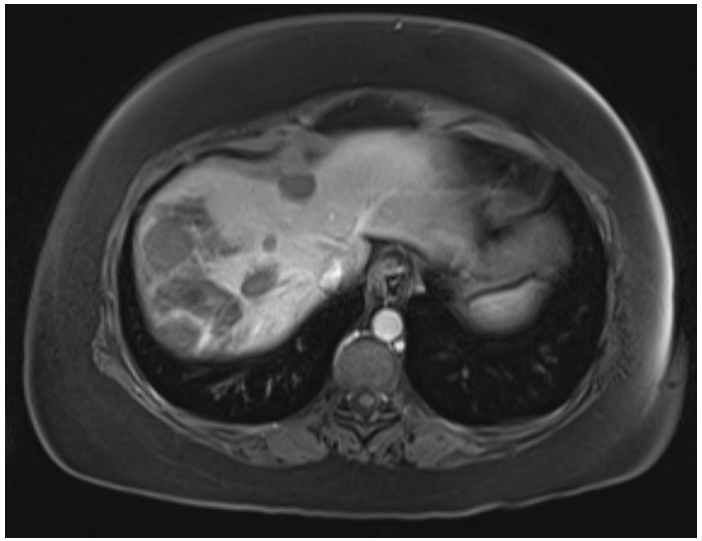
Tumor Exposure → 400X Vs Systemic

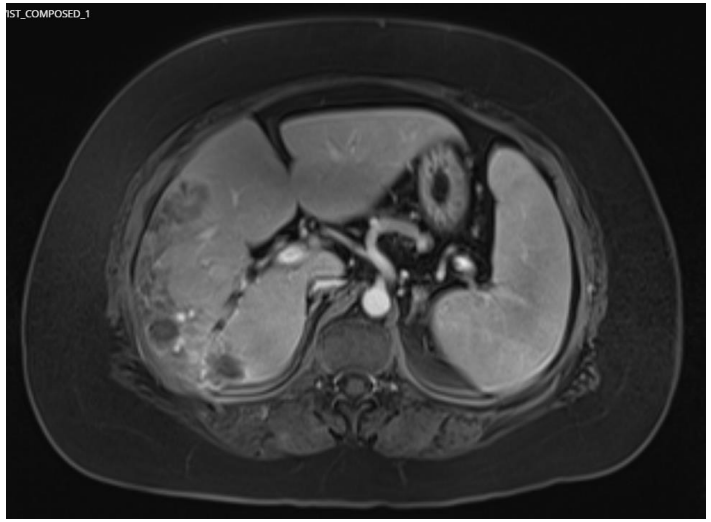
Biliary Sclerosis Rate= 4-8%

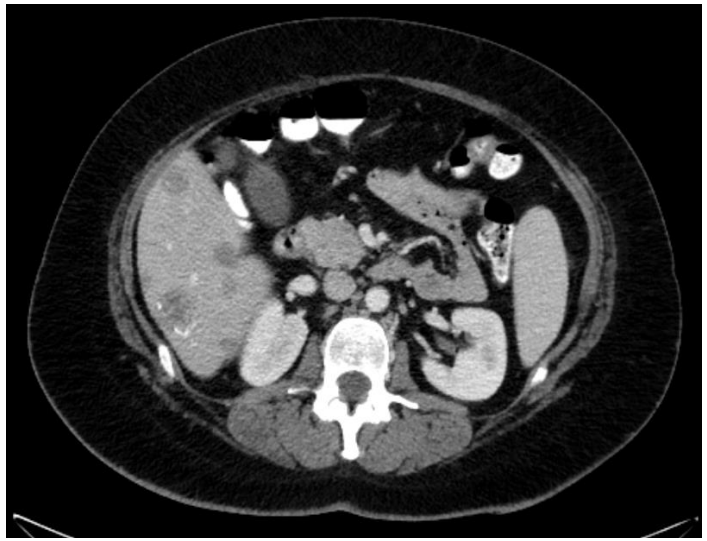


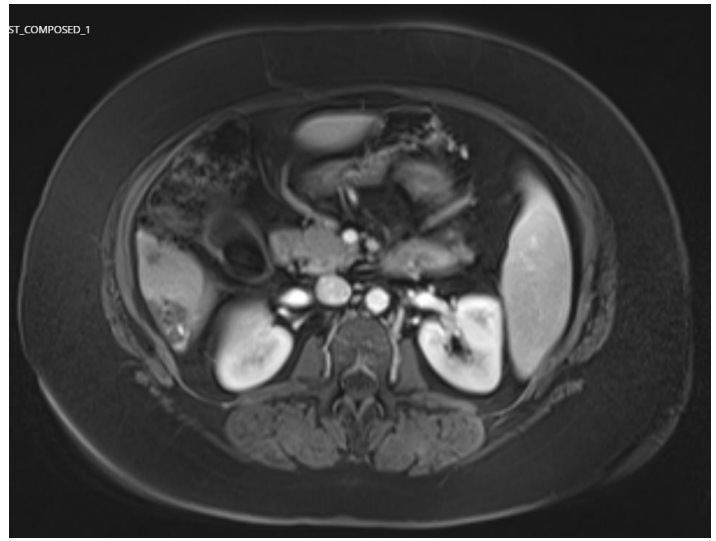
Resectable or Unresectable?



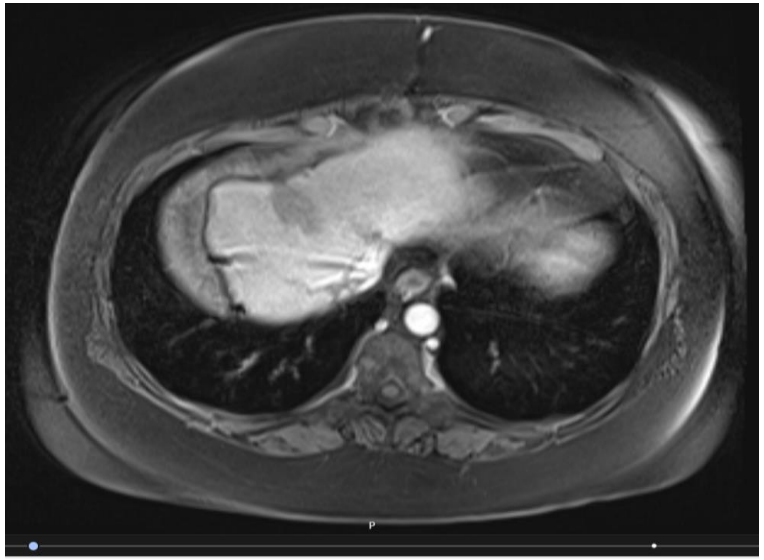


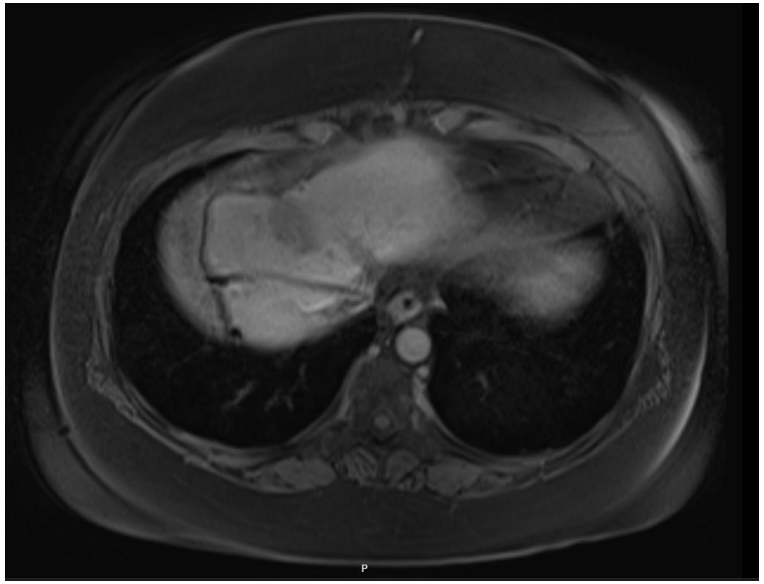


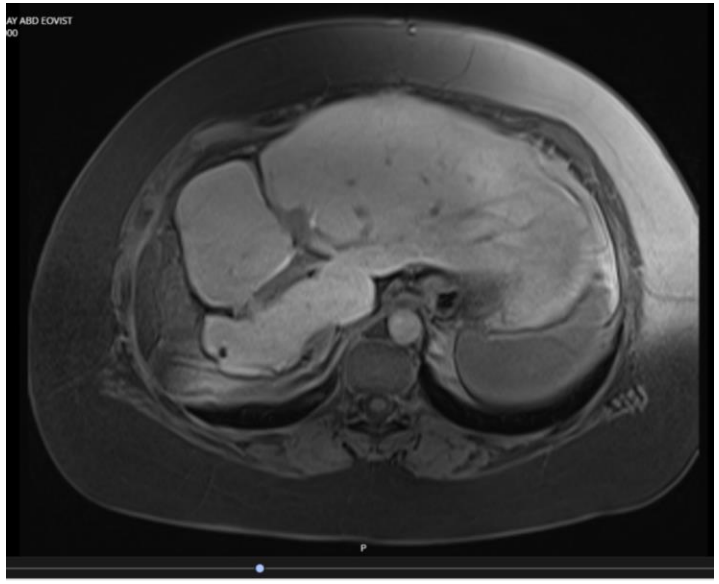




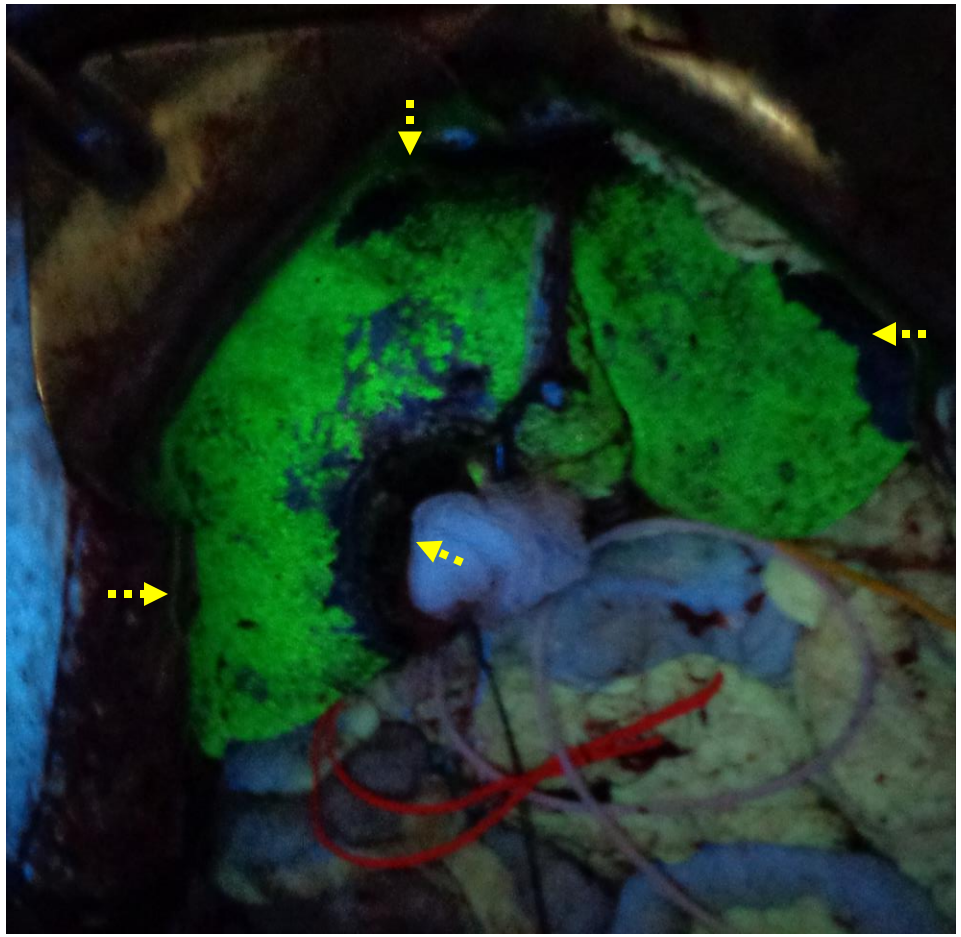
Resection + HAI Pump



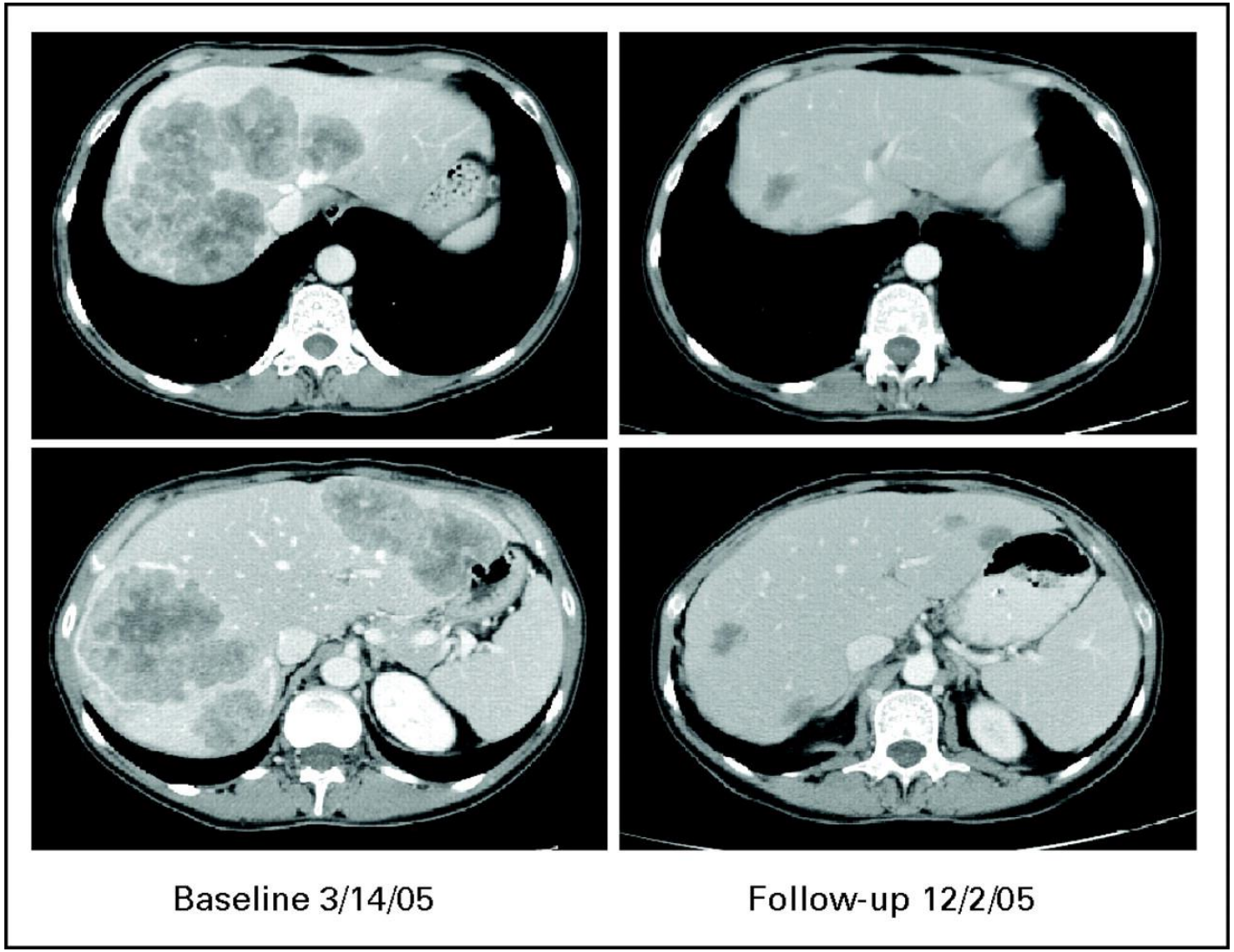




Post Resection: Multiple partial resections (8 tumors)



Conversion to Resectability → HAIP FUDR + systemic oxali + irinotecan



47% of all patients: **Completely resected**

57% of all treatment naive: **Completely Resected**

Multicenter Trial Optiliv. *Ann. Oncol.* **2016**, *27*, 267–274

HAI + FOLFIRINOX+ Cetuximab → 40.6 % RR → 29.7% Resectable

HAI +FOLFIRINOX >> HAI + OXALI
35.6 % Vs 16.7%

J Clin Oncol 27:3465-3471, 2009

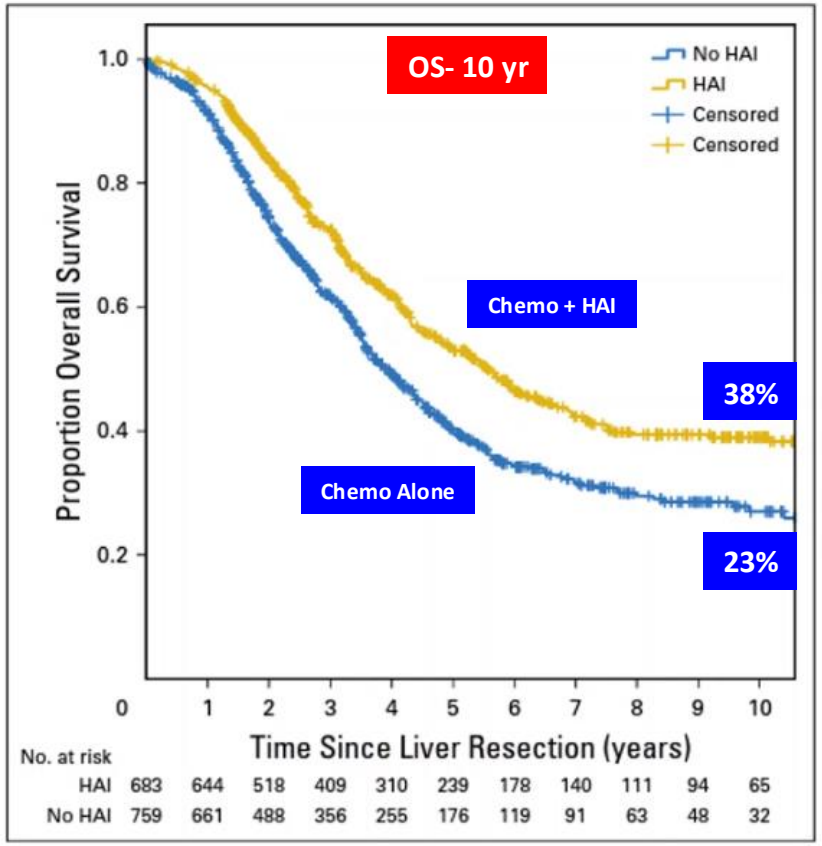
CRLM- Perioperative Chemo + HAI

1992-2012: n= 1442

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

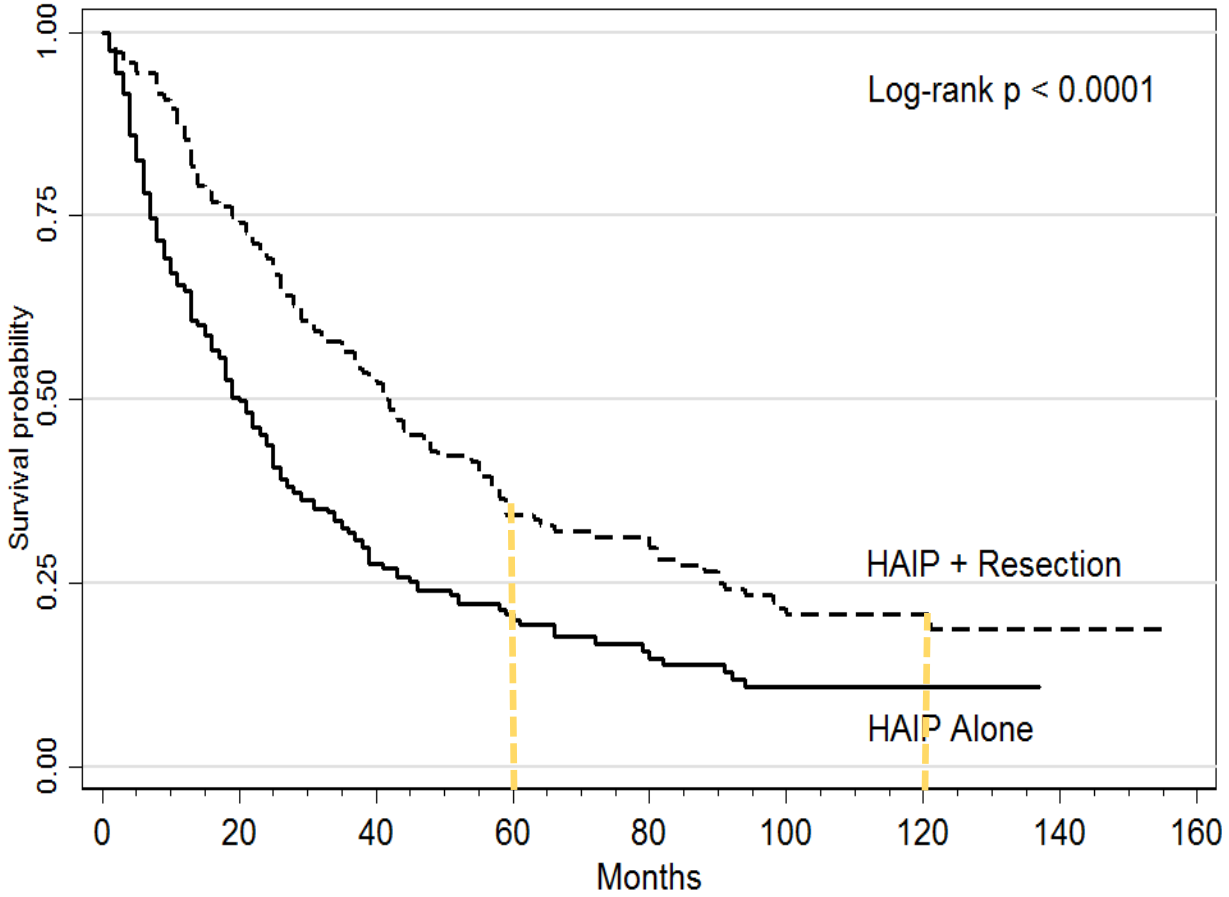
Perioperative Hepatic Arterial Infusion Pump Chemotherapy Is Associated With Longer Survival After Resection of Colorectal Liver Metastases: A Propensity Score Analysis

- Report out of MSKCC, reviewed 2368 patients who underwent complete resection of CRLM, median follow up 55 mo; included patients from 1992-2012
- Modern chemotherapy era (n=1442 pts): median OS **67 months** with HAI vs **47 months** without HAI, HR **0.67**



All patients underwent a curative-intent resection of colorectal liver metastases. Patients who did not receive modern systemic chemotherapy were excluded. The median overall survival was 67 months with hepatic arterial infusion pump chemotherapy (HAI) and 47 months without HAI ($P < .001$).

Hepatic Artery Infusion- California Cancer Registry



Survival data available for 344 patients (98.6%)

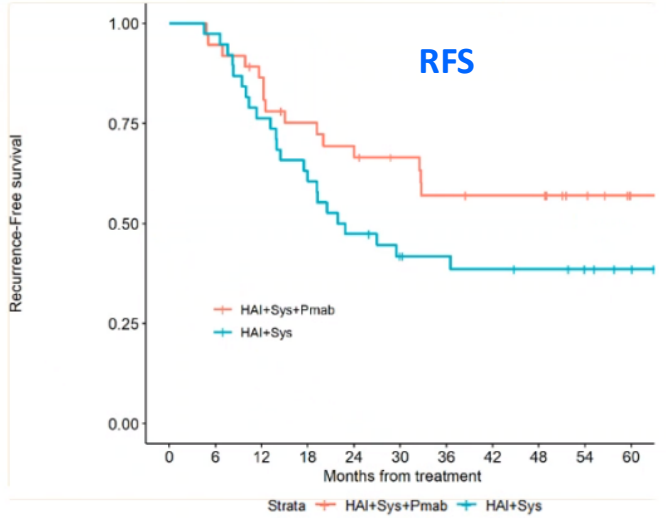
Liver Resection Synchronous with Hepatic Arterial Infusion Pump (HAIP) for Colorectal Cancer Liver Metastases: Results alone or with Liver Resection.
I. Konstantinidis.....**G. Singh.** Regional Cancer Therapies Meeting.2/2017.

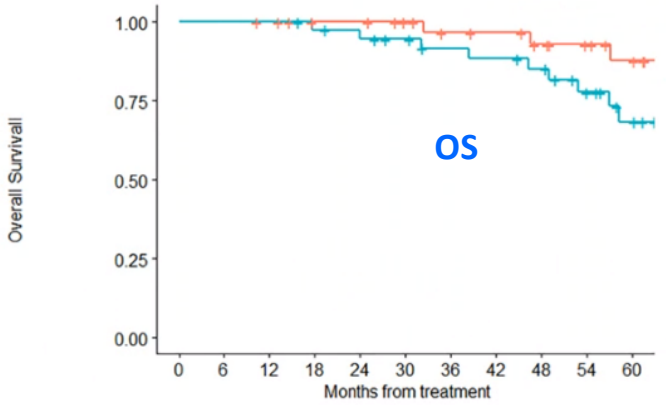
LESSONS LEARNT- HAIP Pump in the Adjuvant setting

Literature

Randomized phase II trial of adjuvant hepatic arterial infusion (HAI) + systemic FOLFIRI +/- panitumumab (Pmab) in patients with resected RAS wild type colorectal cancer hepatic metastases (CRLM).

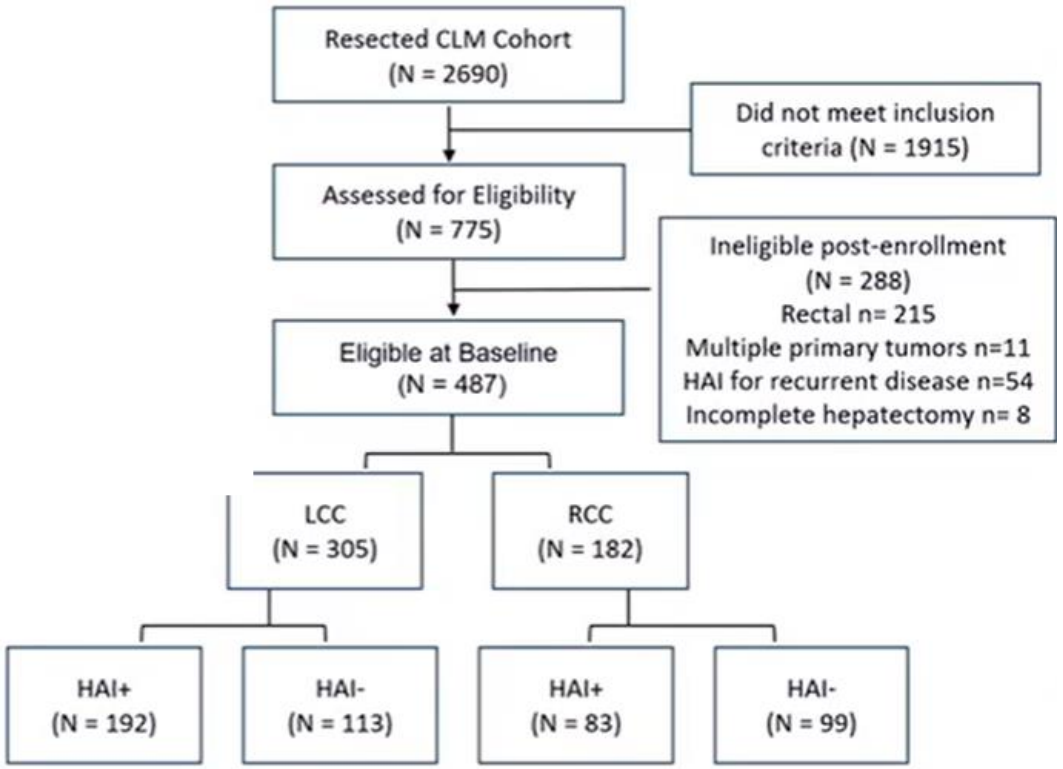
- NCT01312857, n=75 pts
- HAI + FOLFIRI +/- Pmab
- 3 yr RFS: **57%** w/ Pmab vs **42%** w/o Pmab
- 3 yr OS: **97%** w/ Pmab vs **91%** w/o Pmab





Ann Surg. 2021 August 01; 274(2): 248–254.

LESSONS LEARNT- Impact of Tumor Laterality & HAIP Pump



Left >> Right

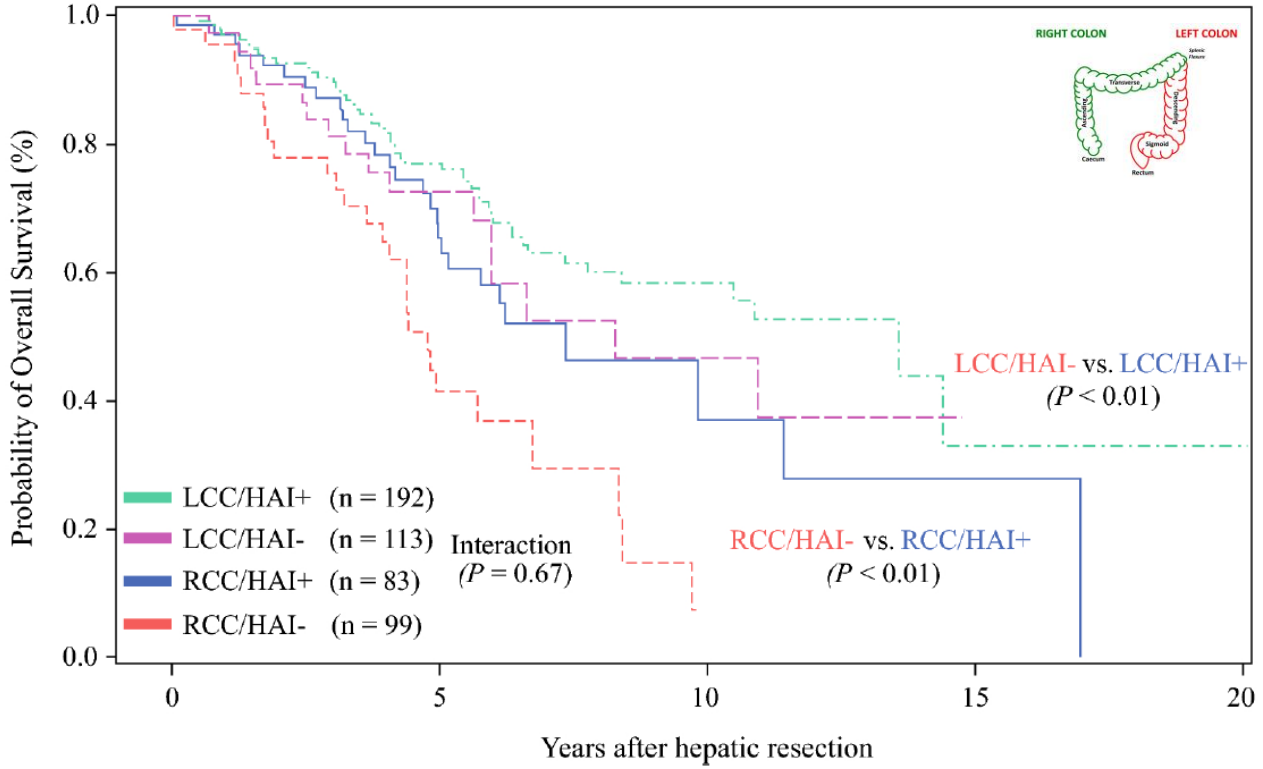


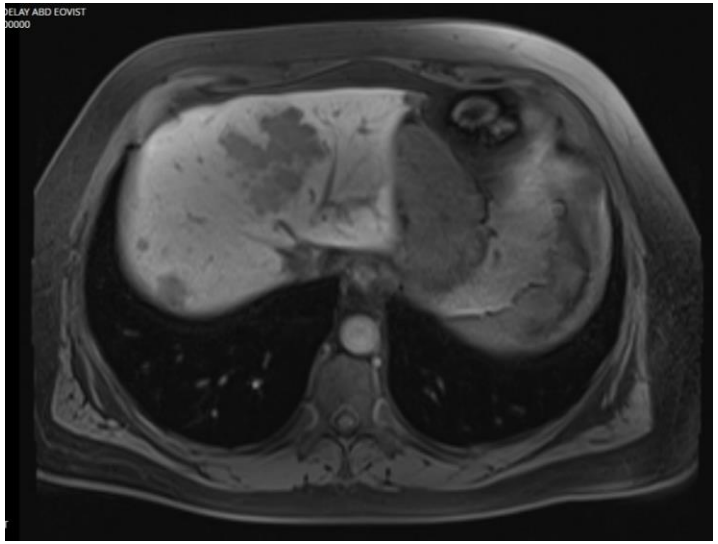
Figure 4.
Overall survival (OS) rates for RCC (right colon cancer) and LCC (left colon cancer) stratified by treatment with (HAI +) and without (HAI −) therapy.

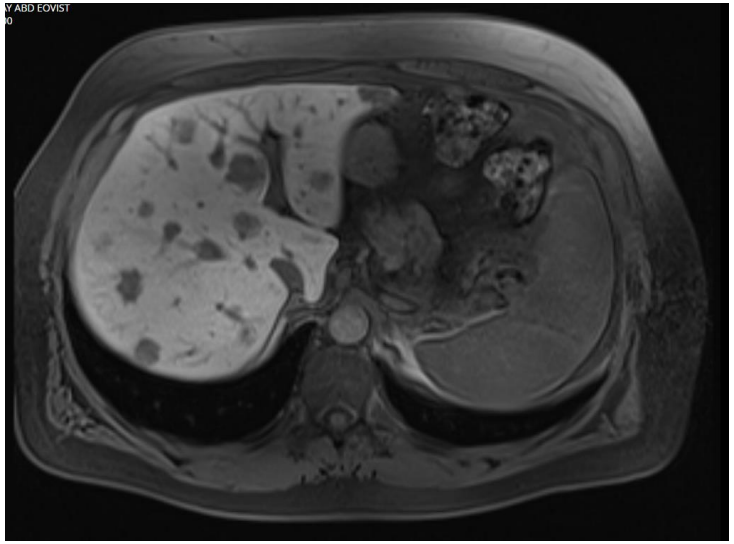
Ann Surg Oncol. 2021 July ; 28(7): 3685–3694.

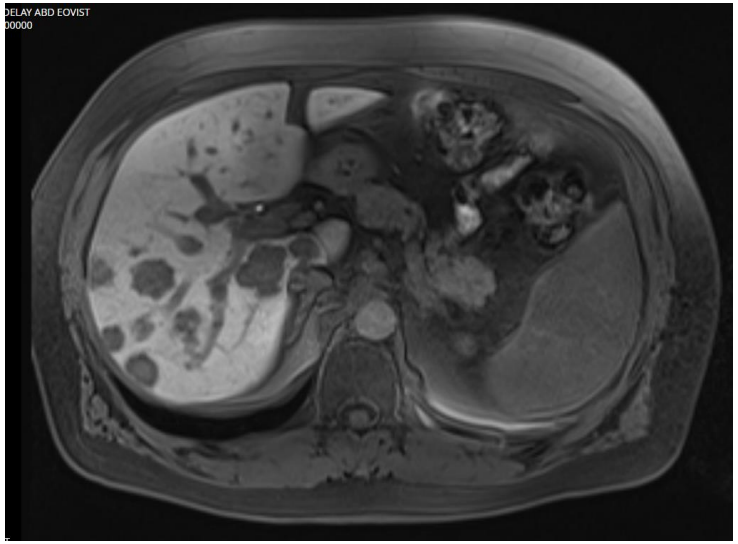
Resectable or Unresectable?

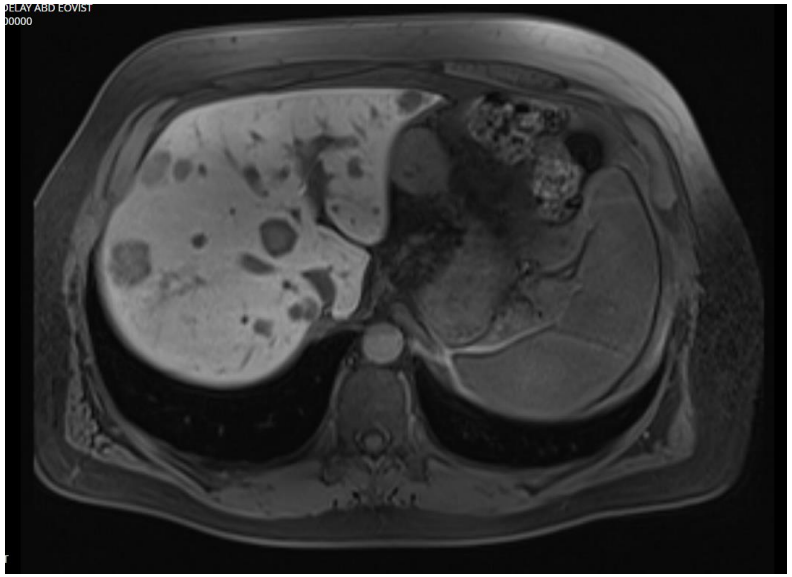
09/23/15

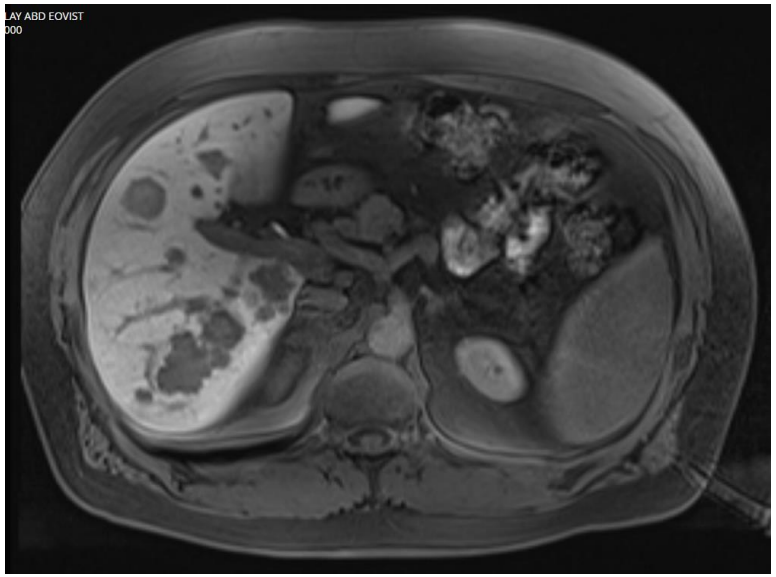
Distinct Entity of Liver Dominant Dz

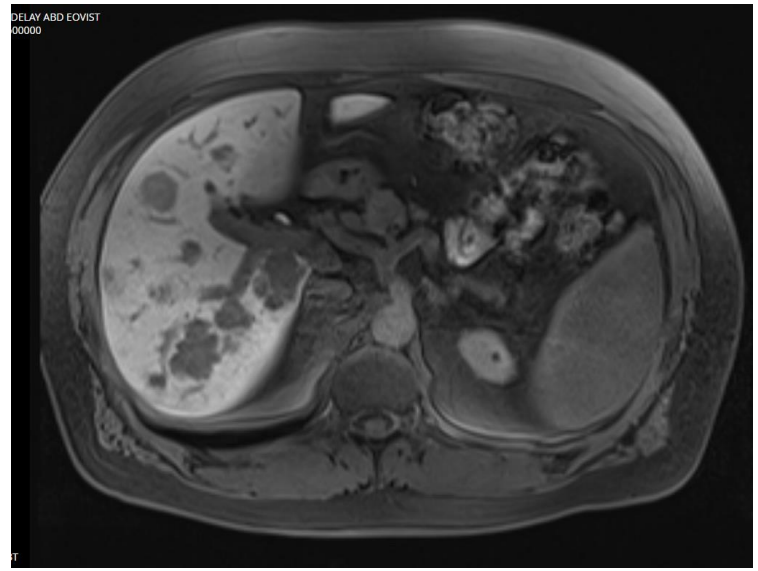








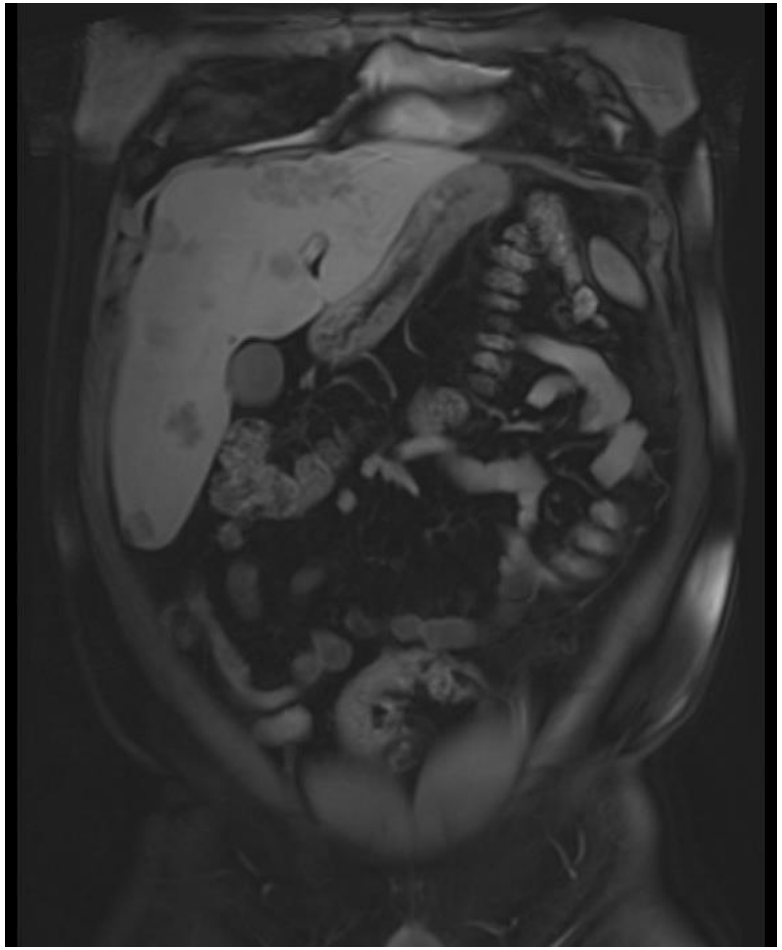


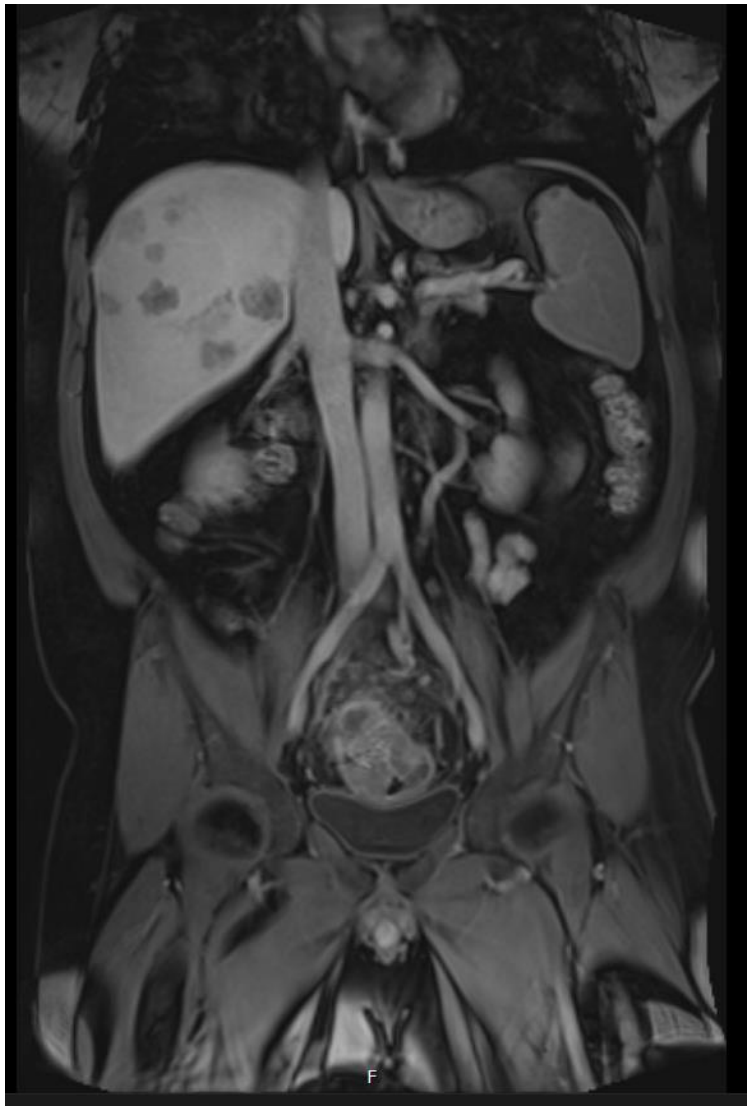


Resectable or Unresectable?

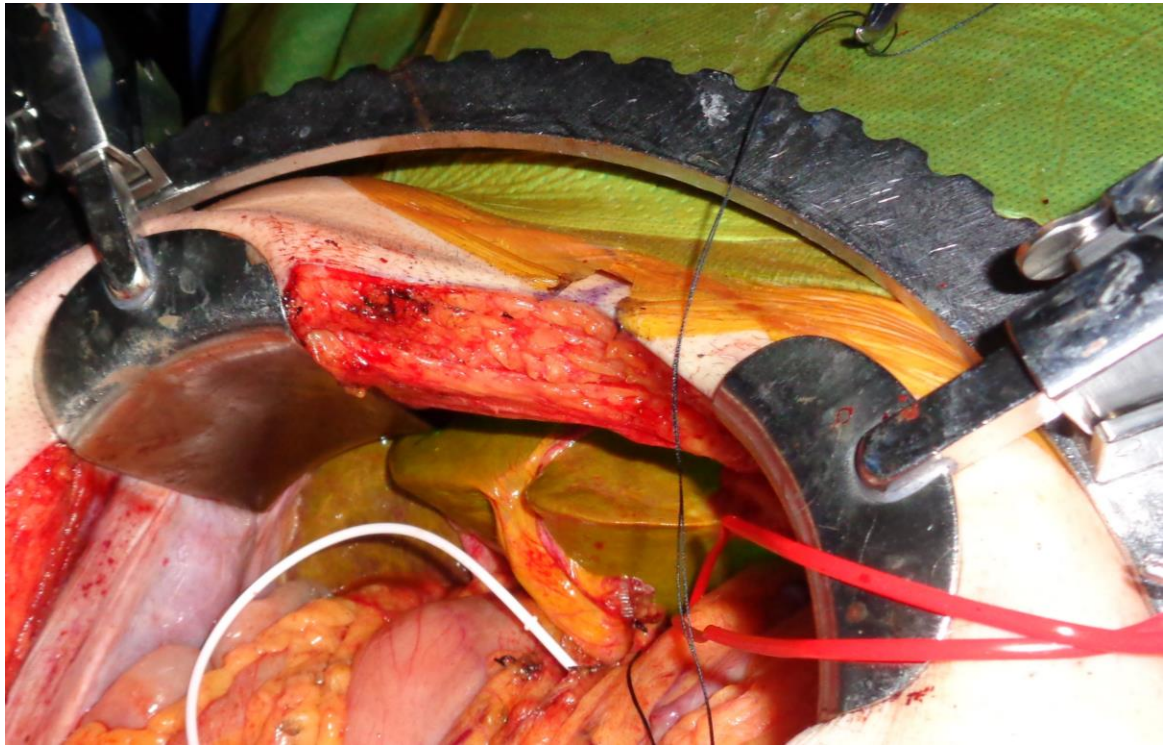
9/23/15

Distinct Entity of Liver Dominant Dz





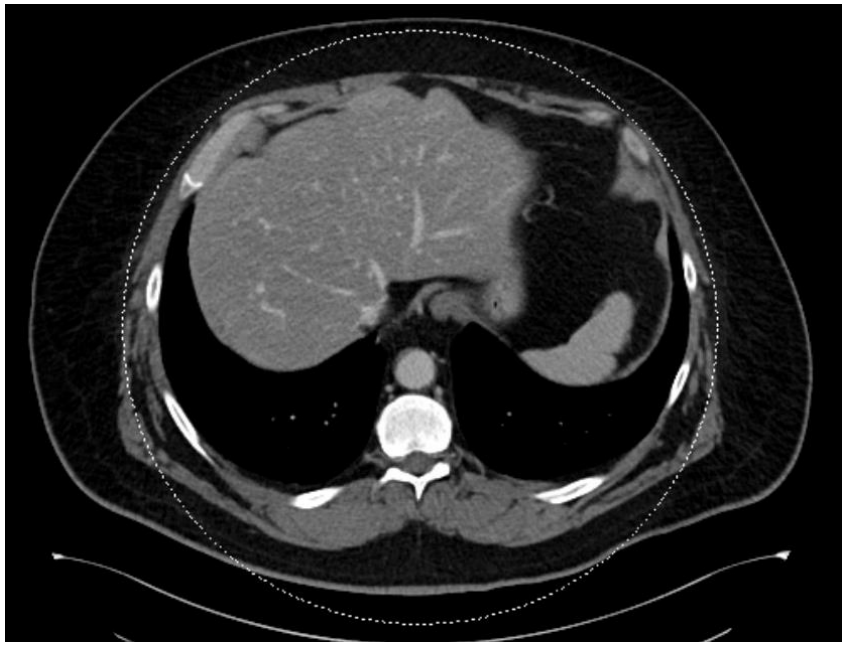
B/L Liver Mets >30: Smaller on Chemo at 3 months- Pump only no resection

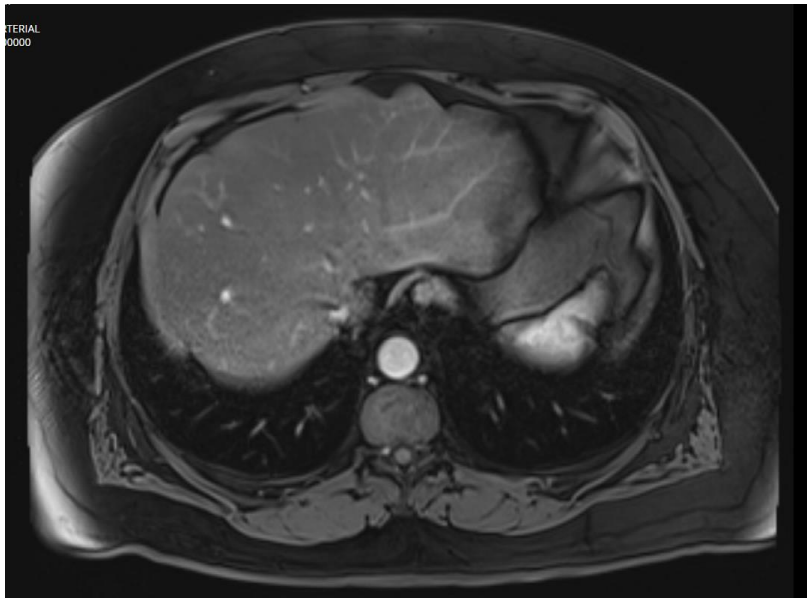


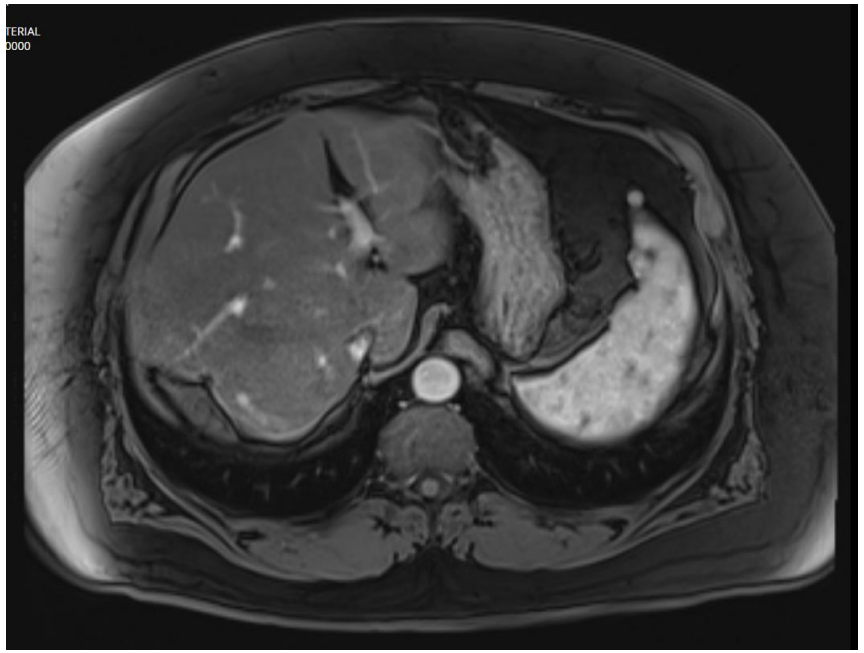
Distinct Entity of Liver Dominant Dz

9 years later

10/27/23



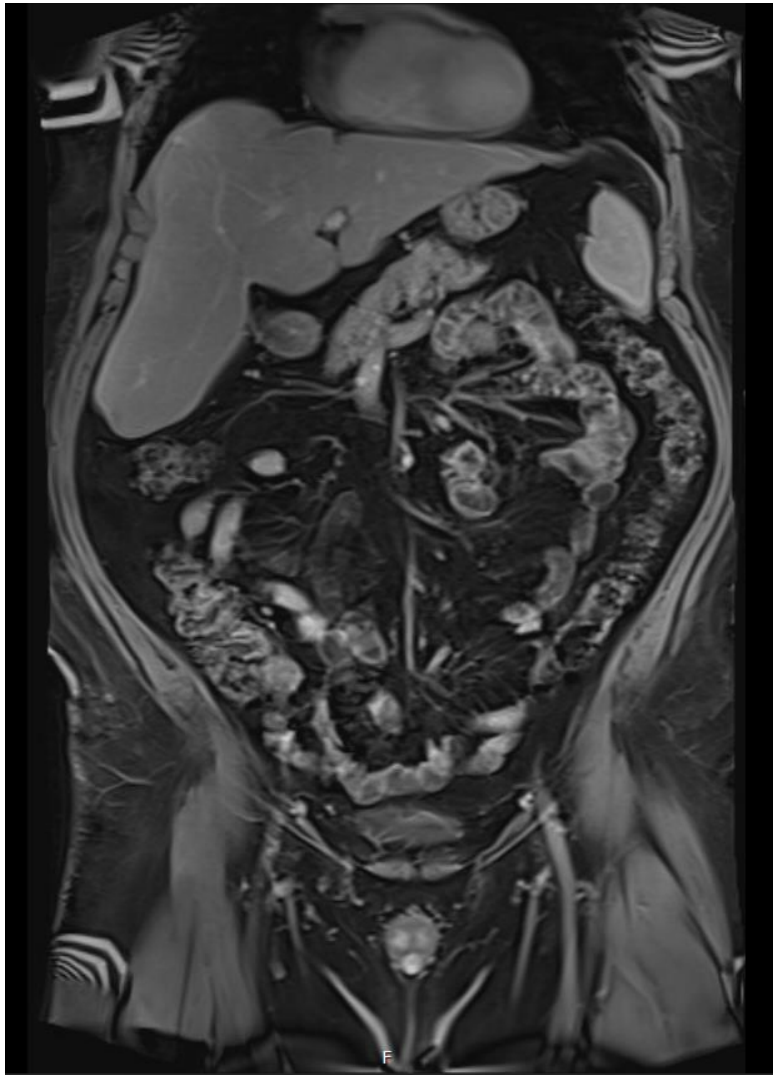


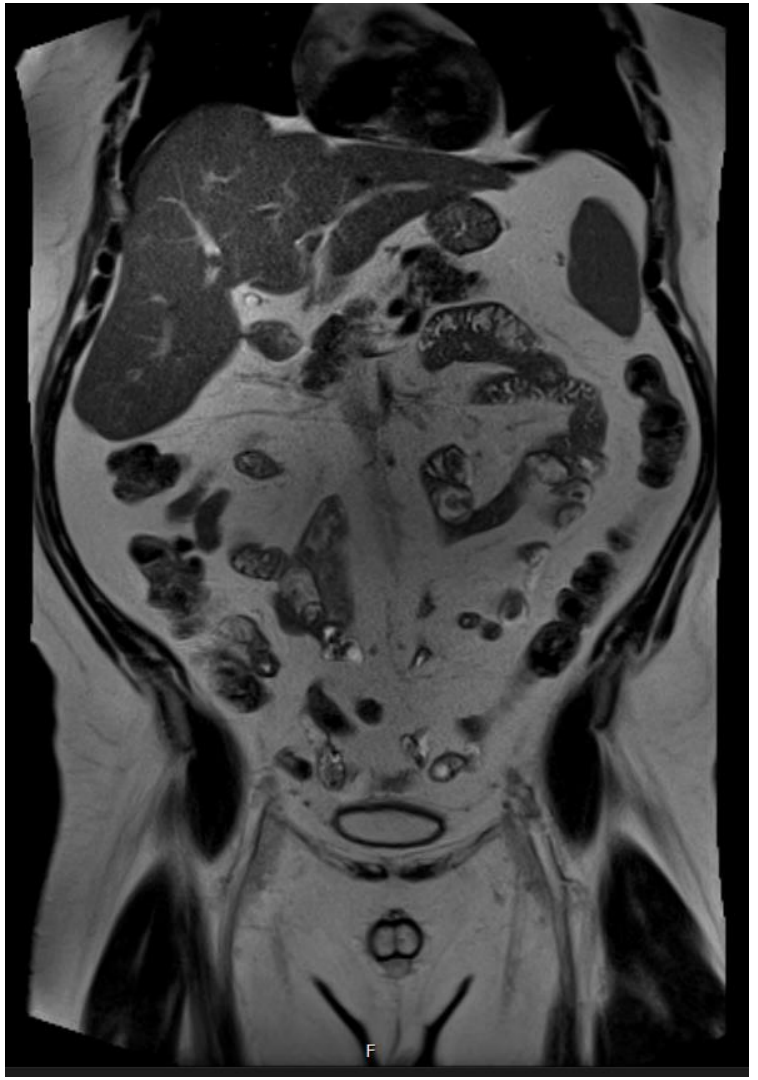


Distinct Entity of Liver Dominant Dz

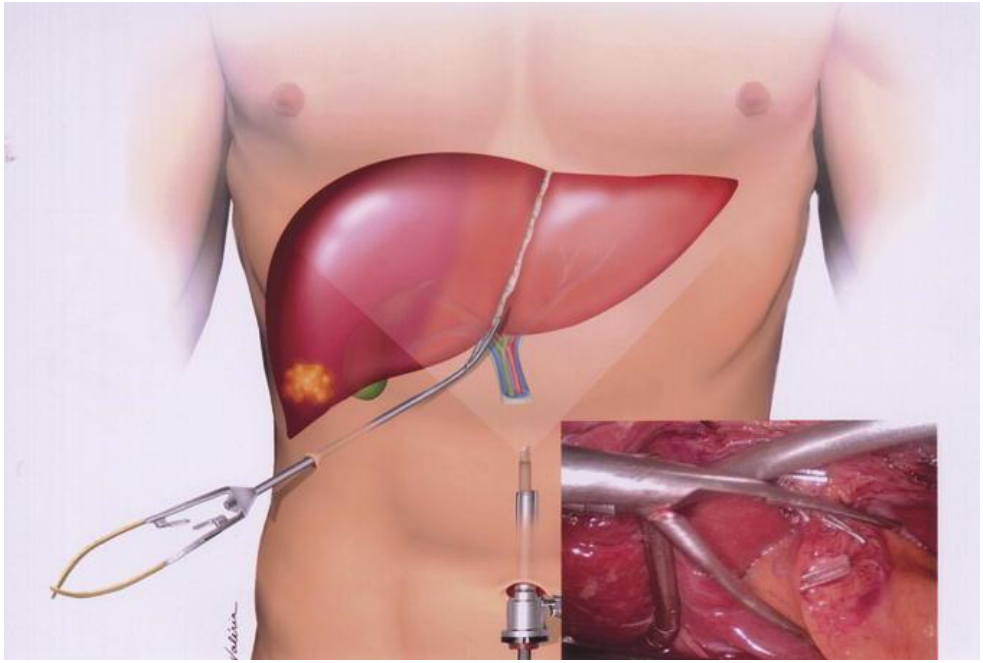
9 years later

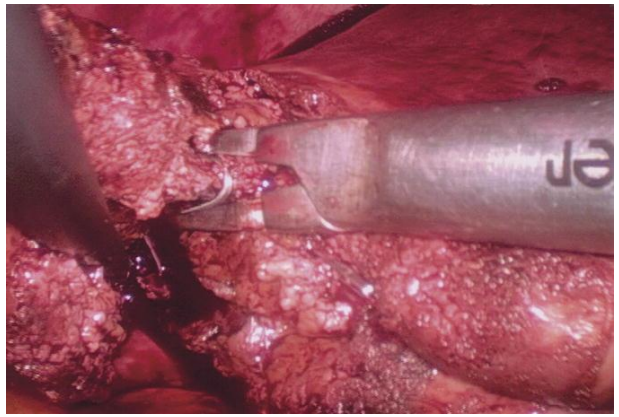
10/27/23

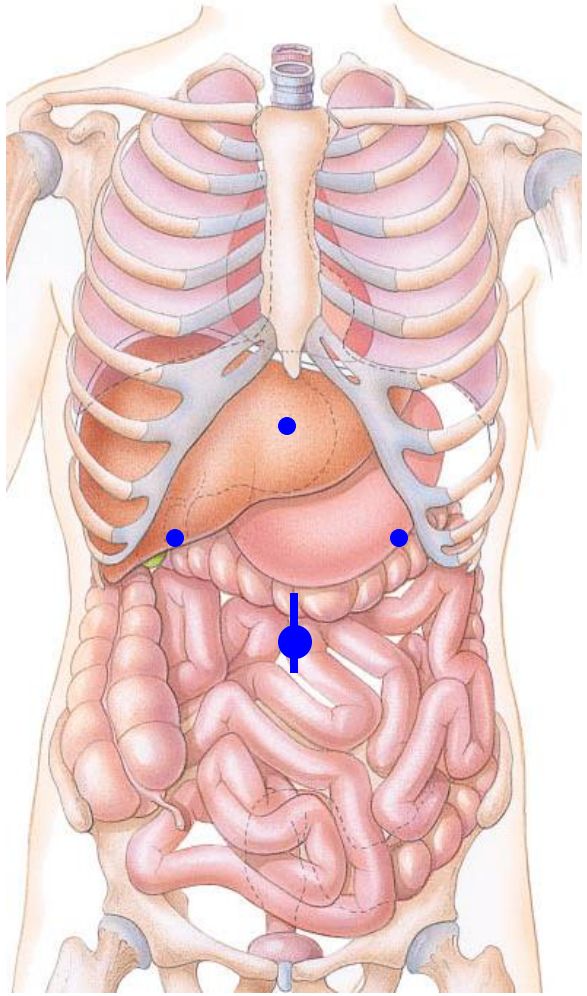




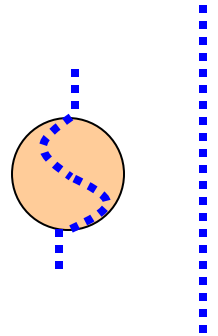
Laparoscopic Liver Resections



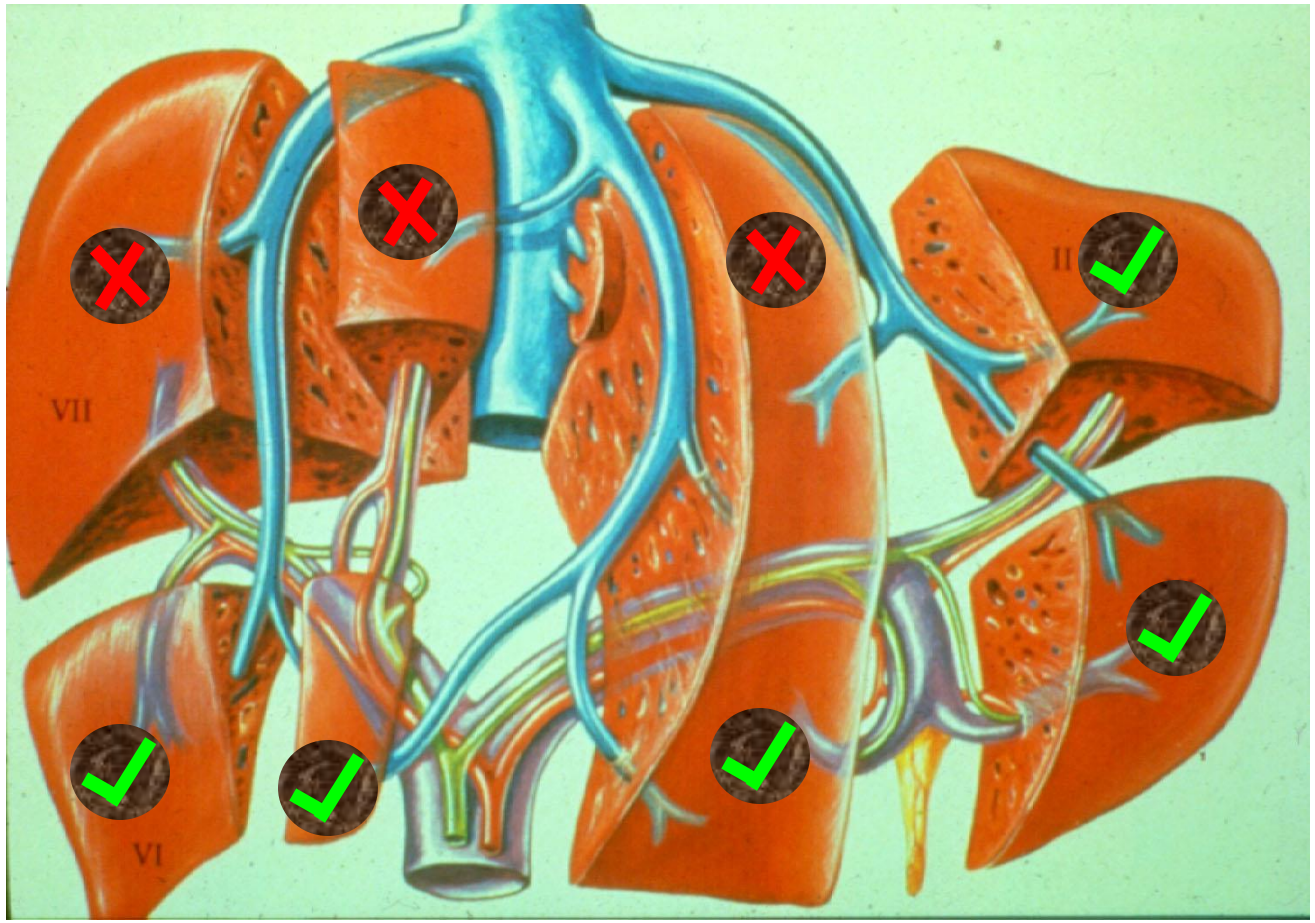


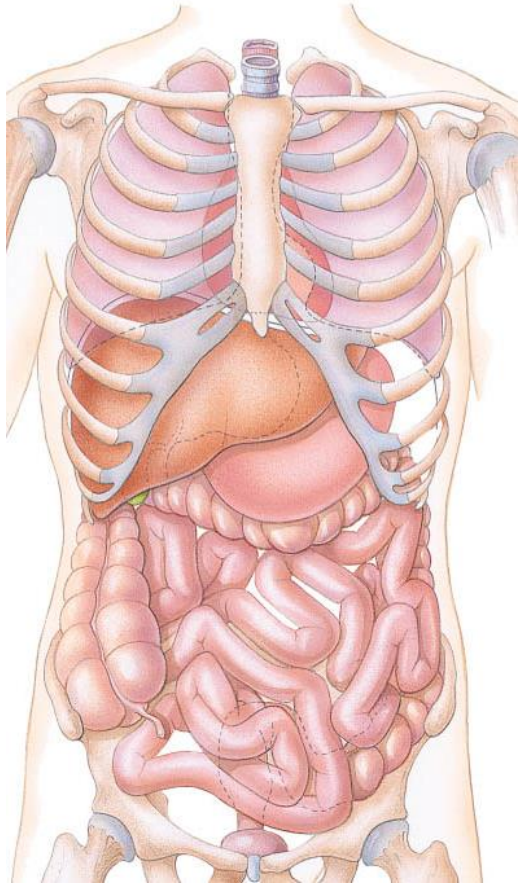


Laparoscopic Right Hepatectomy



Resection Plans for Laparoscopic Resections





Meet the Parents
Mr. & Mrs. Robot

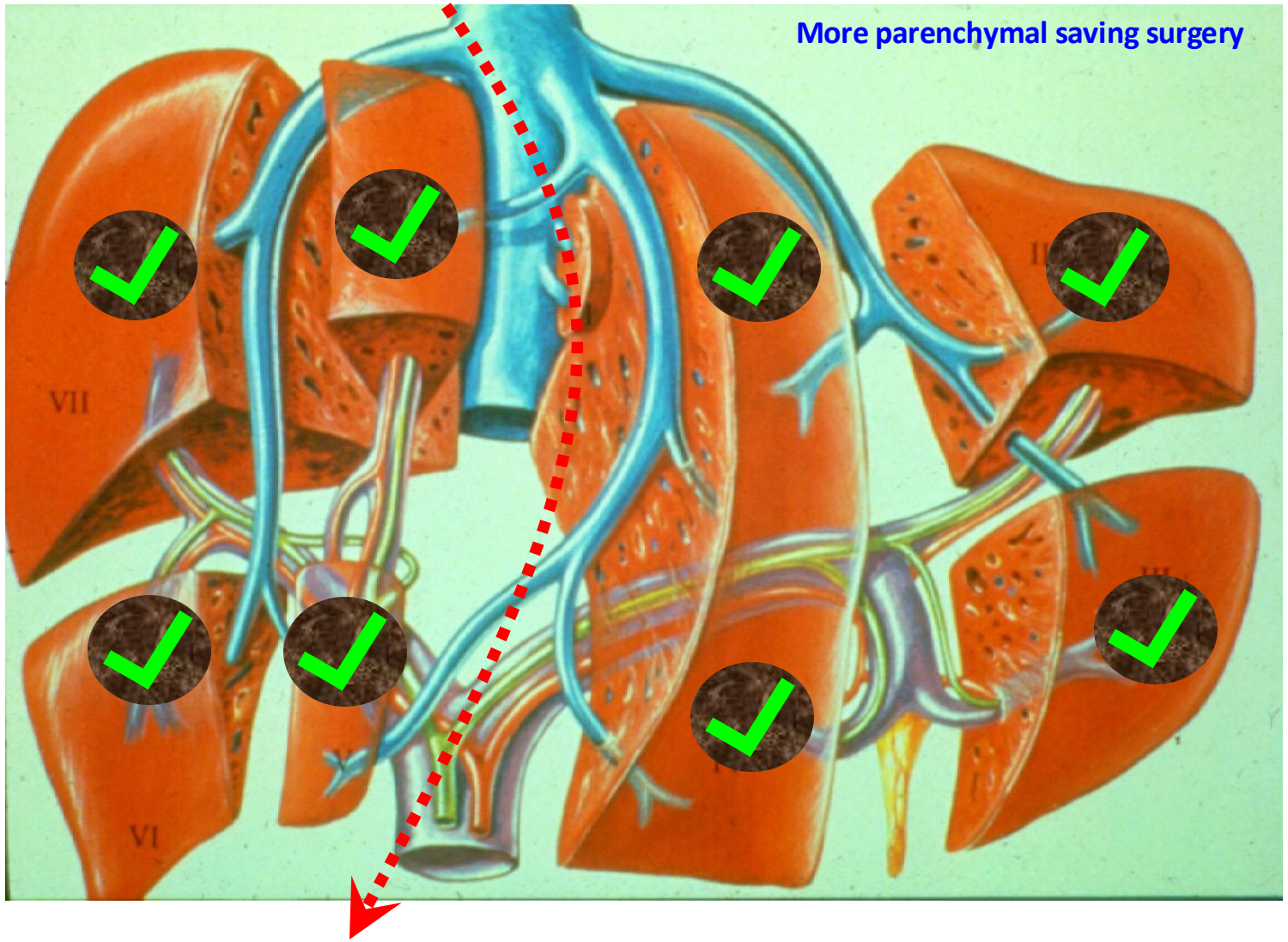
da Vinci Xi

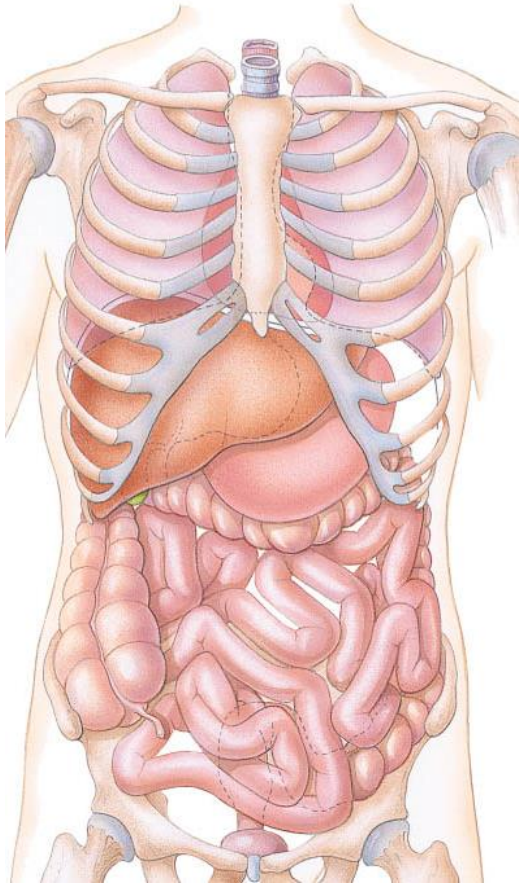
da Vinci 5

Is much BETTER- but must be used judiciously

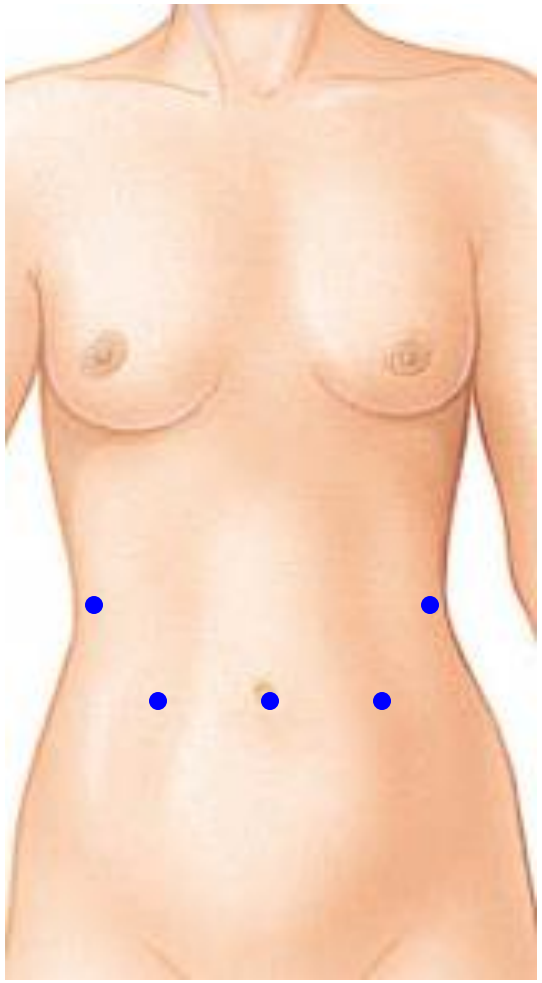
Perfect Cases for the Robot

Clear Advantage over Laparoscopic





Port Sites for Liver Resection



Split Leg if Supine

Summary- Minimally Invasive Liver Resections

Is Robotics/ MIS the future of Surgery?

YES

Are we there today?

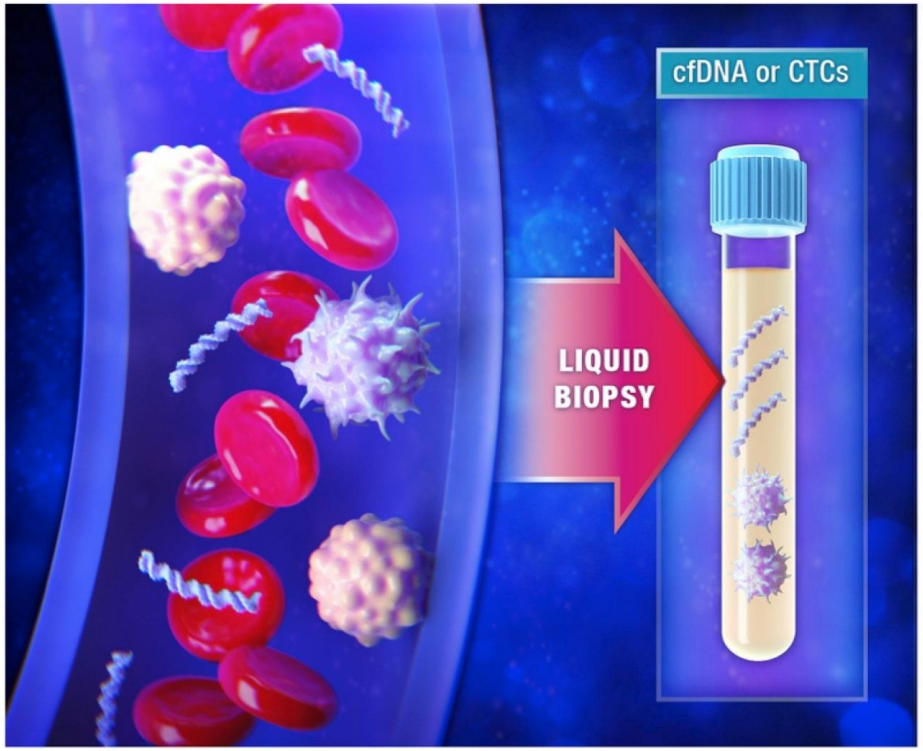
Getting there

Does that mean we stop trying?

NO

EVERYTHING IS GOING TO CHANGE

Liquid Biopsy



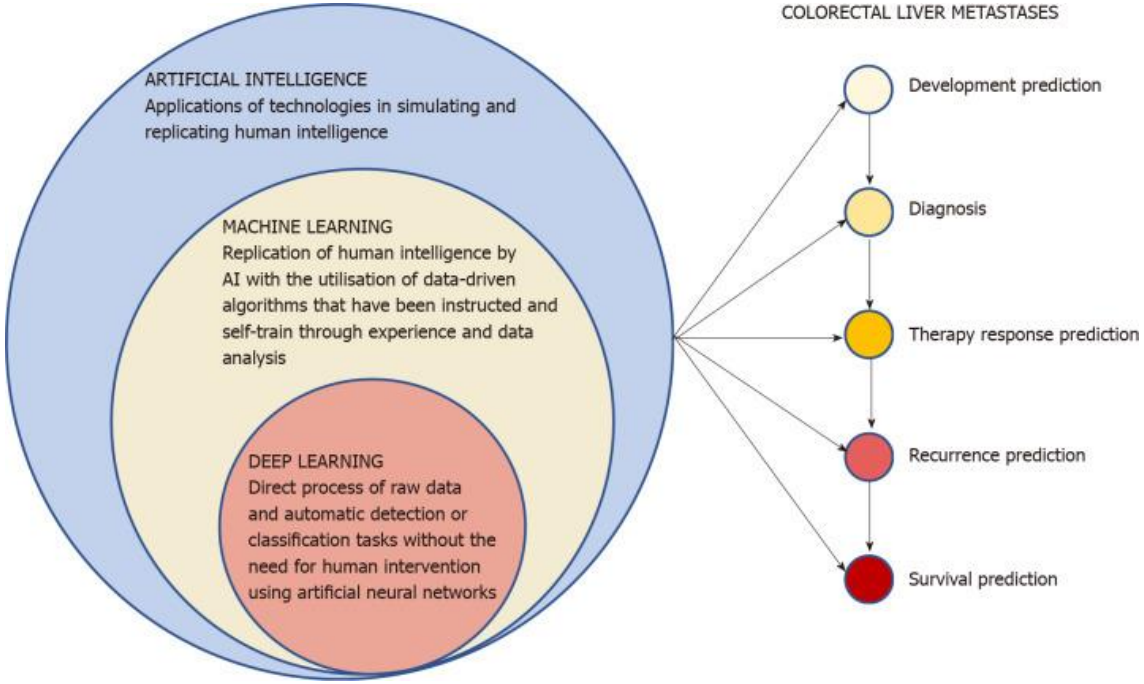
DIAGNOSIS:
Genotyping cfDNA in the blood to determine the tumor profile

RESPONSE AND FOLLOW UP:
Analysis of cfDNA and CTC for real time monitoring of response to treatment

TUMOR EVOLUTION:
Emergence of molecular alterations associated with resistance to therapy

MINIMAL RESIDUAL DISEASE:
The presence of cfDNA or CTC in the circulation indicates that the disease is still present

Artificial Intelligence



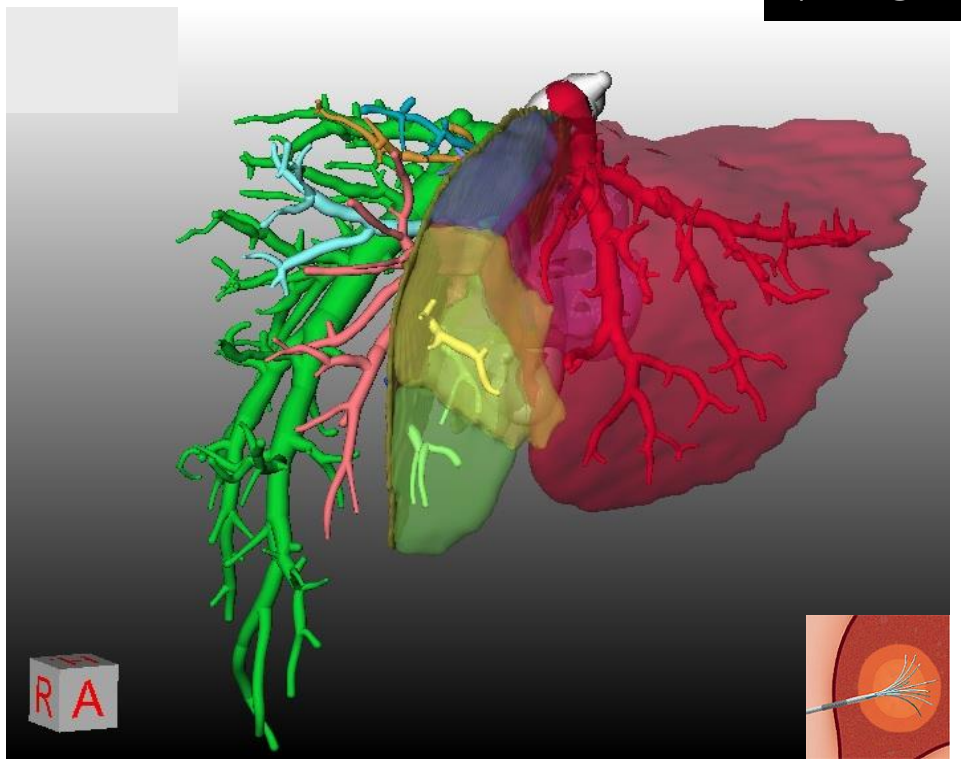
World J Gastroenterol. 2022 Jan 7; 28(1): 108–122.

Summary: Resection the Gold Standard

Paradigm Shift

What is Removed **BUT** **What is Left Behind**

MRI IS A MUST

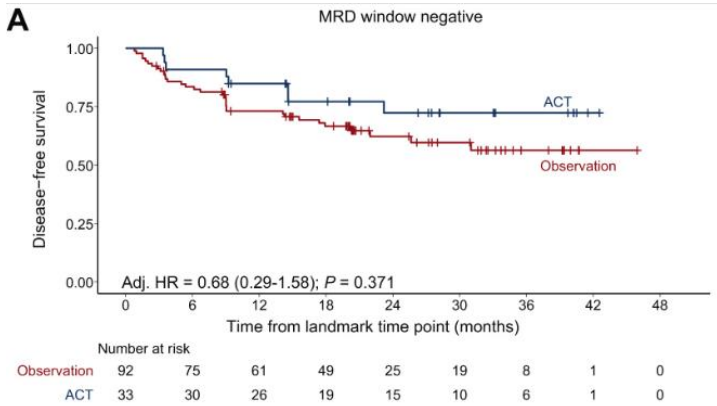


- Future Liver Remnant of 20% (30%)
- Adequate Inflow and Outflow
- At least 2 Contiguous Segments
- Capability of Resecting all visible Dz
- MWA/ IRE/ RFA/ Nanoknife is an Adjunct or Compliment
- Ablation/ SBRT for <3 cm masses acceptable

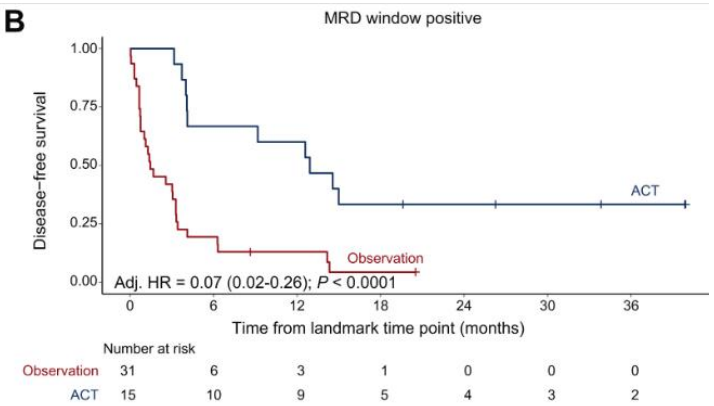
Question is no longer 'WHO IS RESECTABLE' but rather 'WHO IS NOT RESECTABLE'

ONLY absolute CONTRAINDICATION to surgery for CRLM is the presence of NON-TREATABLE DISEASE ELSEWHERE

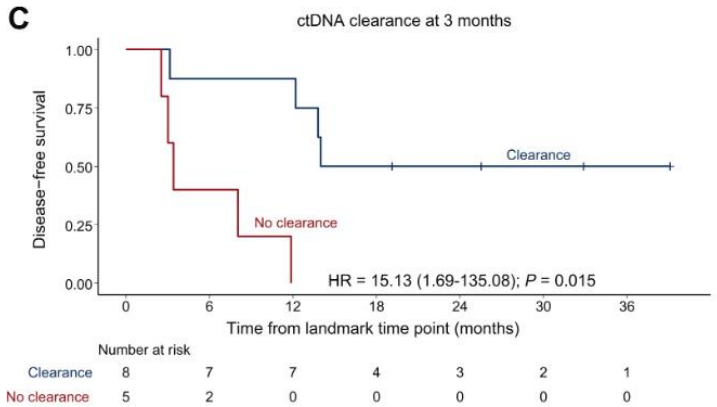
Survival benefit of adjuvant chemotherapy based on molecular residual disease detection in resected colorectal liver metastases: CIRCULATE-Japan GALAXY



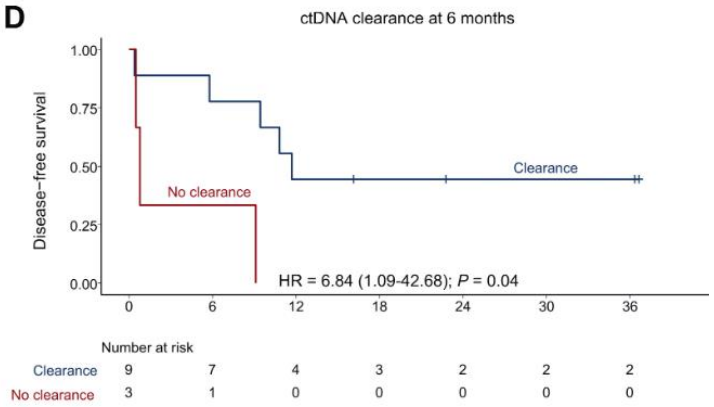
ctDNA status	ACT	Observation
Events %	24.24 (8/33)	35.87 (33/92)
24 month DFS % (95% CI)	72.31 (51.43-85.38)	62.22 (50.11-72.18); P = 0.384
mDFS (months)	NR	NR (25.6-NR)



ctDNA status	ACT	Observation
Events %	66.67 (10/15)	93.55 (29/31)
24 month DFS % (95% CI)	33.33 (12.2-56.4)	NE
mDFS (months)	12.92 (4.11-NR)	1.45 (0.76-3.32)



ctDNA status	Clearance	No clearance
Events %	50 (4/8)	100 (5/5)
24 month DFS % (95% CI)	50.0 (15.20-77.50)	NE
mDFS (months)	14.0 (13.80-NR)	3.42 (3.02-NE)



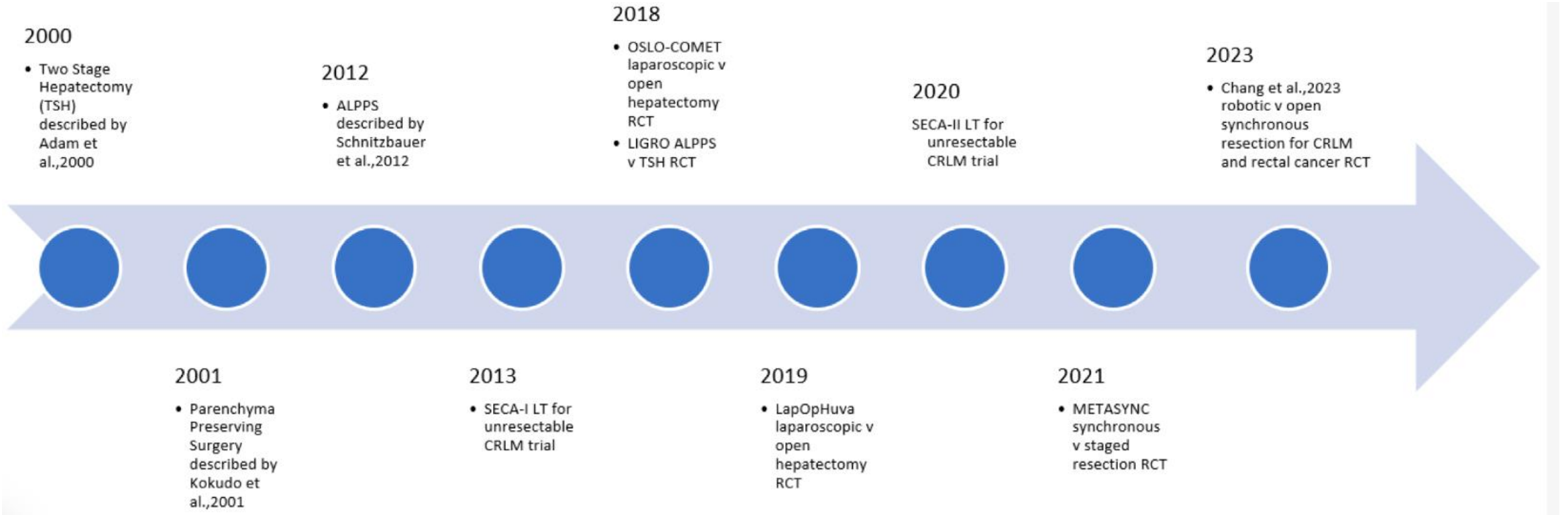
ctDNA status	Clearance	No clearance
Events %	55.56 (5/9)	100 (3/3)
24 month DFS % (95% CI)	44.40 (13.60-71.90)	NE
mDFS (months)	11.70 (9.43-NR)	0.79 (0.49-NE)

MRD Negative- Recur in Lungs

MRD Positive- Recur in the Liver

Annals of Oncology, 2024

Summary: Key SURGICAL Techniques in CRLM



Summary: Key Surgical Adjuncts with Local & Systemic Options