Practical approach to Colorectal Liver Metastases

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CARE + RESEARCH
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UBC THE UNIVERSITY OF BRITISH COLUMBIA

Disclosure

- Ipsen Biopharmaceuticals Canada
  - advisory board honorarium

Disclosure

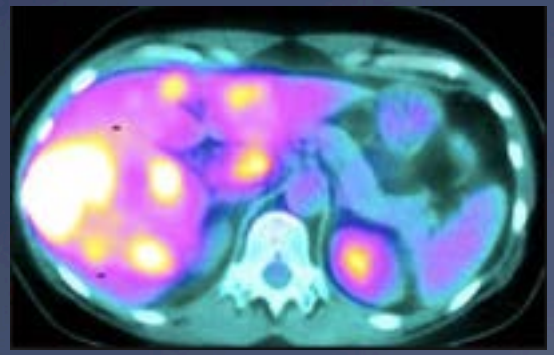
- Managing conflict of interest
  - Not applicable here

Outline

- Improvements in treatment of CRLM
- Extended criteria for resection
- What should/can be done before referral
- When to refer to HPB center
- Outcomes of liver resection
- Common postop complications after liver resection

Colorectal Liver Metastases (CRLM)

- The liver is the most common site for hematogenous metastasis
- 25% of patients with primary CRC present with synchronous hepatic metastasis
- Nearly 50% patients will eventually develop metachronous liver metastases



Dramatic improvements in prognosis

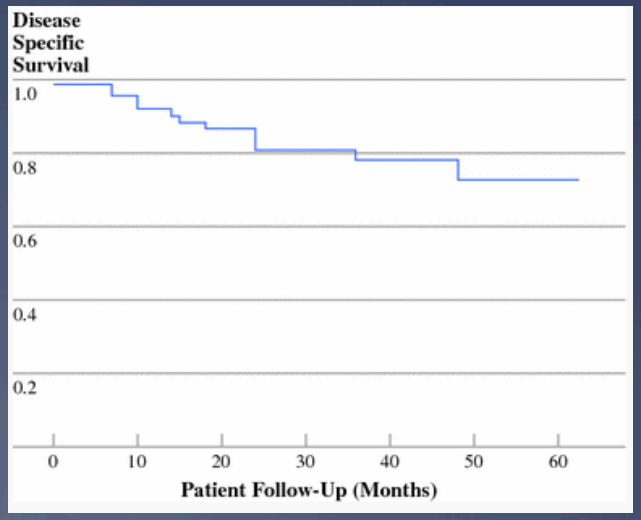
Dramatic improvement from the seminal study by Foster (1978)

* **5-year survival was 20%.**

With newer multimodal treatments and careful patient selection **5-year survival approaching 70%** can be achieved after resection (Nikfarjam et al, 2009)

TABLE III Liver Resection for Metastatic Colorectal Cancer: Operation versus Survival

	Lobectomy	Segmental Resection	Wedge
Patients	46	25	97
Operative deaths	5	0	3
5 year survivors	6/45 (13%)	5/24 (21%)	22/93 (24%)



Resection makes a difference

Wood and colleagues (1976)

* Very few patients had resectable disease;
* 1-, 3-, and 5-year survival of these untreated patients were 77%, 23%, and 8%, respectively, compared with 15%, 0%, and 0% for the unresectable group.

Similarly, Wagner and colleagues (1984)

-3- and 5-year survivals for untreated resectable disease of 14% and 2%, respectively, compared with 4% and 0% for patients with unresectable disease.

VOLUME 25 · NUMBER 29 · OCTOBER 10 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Actual 10-Year Survival After Resection of Colorectal Liver Metastases Defines Cure

James S. Tomlinson, William R. Jarnagin, Ronald P. DeMatteo, Yuman Fong, Peter Kornprat, Mithat Gonen, Nancy Kemeny, Murray F. Brennan, Leslie H. Blumgart, and Michael D'Angelica

- Of 612 consecutive patients in a 10 year follow up period, 102 actual 10-year survivors, 1985 to 1994
- Patients who survive 10 years appear to be cured of their disease
- In well-selected patients, 1 in 6 chance of cure after hepatectomy for CLM. The presence of poor prognostic factors does not preclude the possibility of long-term survival and cure.

Better Patient Selection

General Health

- Identification and management of co-morbidities
- Cardiac disease
- Pulmonary disease
- Renal disease

Liver Health

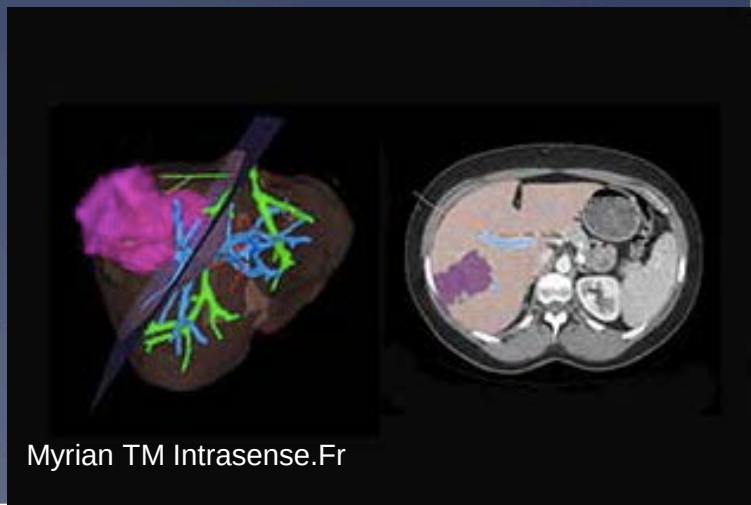
- Understanding and management of primary liver disease or dysfunction
- Cirrhosis/NASH/Chemo induced liver injury
- Portal HTN
- Synthetic dysfunction
- Cholestatic disease

Tumor Factors

- Better preoperative imaging
- Better preoperative planning
- Laparoscopic staging

FIGURE 2.

Computed tomography 3-D reconstruction before surgical showing liver metastases



Myrian TM Intrasense.Fr

Stratifying patients with CRLM

Four large studies with robust design of useful predictive models for favorable survival after metastasectomy

1. Nordlinger and colleagues (1996): multicenter series of more than 1500 patients.

2. Fong and colleagues (1999): single institutional series of 1001 patients

3. Kattan et al 2008 reported on a cohort of 1477 patients (Kattan et al, 2008)

4. Rees and colleagues (2008) evaluated long-term survival in 929 patients from United Kingdom.

Table 3 **Prognostic Variables for Hepatic Colorectal Metastases**

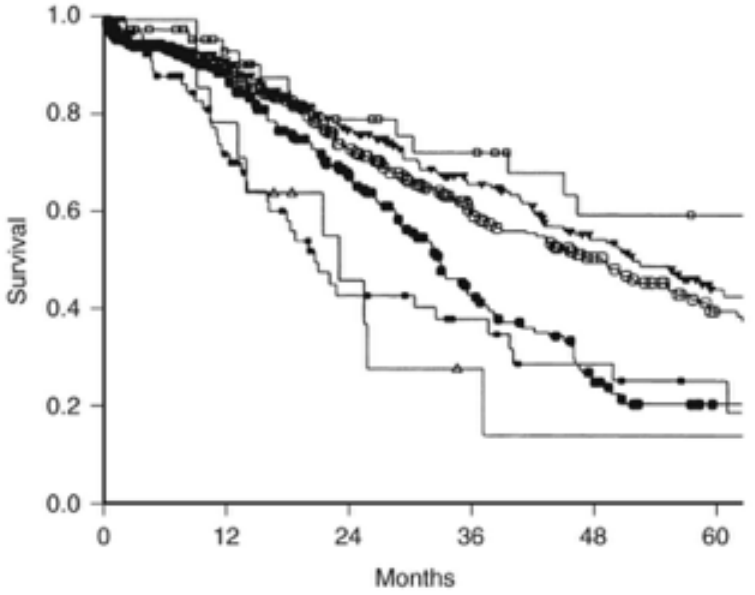
Clinical Indicators	Author
[a]Node-positive primary tumor [a]Disease-free interval less than 12 mo from primary [a]Size of largest lesion > 5 cm [a]More than one tumor [a]Carcinoembryonic antigen level > 200 ng/dL Extrahepatic disease Response to chemotherapy Fibrotic response to chemotherapy	Poultsides 2012[36]
Pathologic Indicators	
Margin-positive resection High TIL cells	Turcotte 2014[37]
Molecular Indicators	
CXCR4 HumanHT-12 gene chip/MRS panel KRAS	Yopp 2012[38] Ito 2013[40] Kemeny 2014[13]

The “Fong Score” - CRS

Fong and colleagues (1999):

- Node-Positive Primary Tumor
- Disease free interval <12 months between colon resection and appearance of metastases
- Size of largest lesion >5 cm
- >1 Tumor
- CEA >200 ng/dL

- Validated by a group in Norway(Mala et al, 2002)

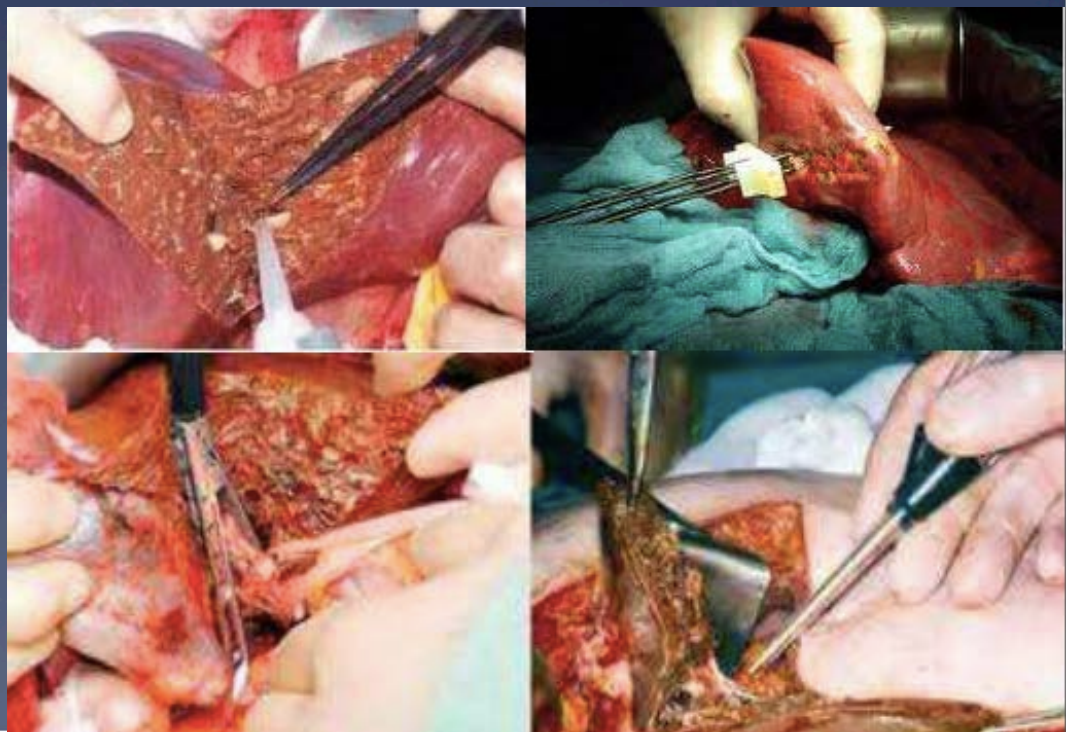


Better surgery for CRLM

- Modern Liver Surgery has Markedly Improved
  - Better operative tools >> Less blood loss and trauma
  - Lower morbidity and mortality
  - Anesthesia care improved
- Better Understanding of Treatable Liver Disease
  - Many lesions →staged or combination procedures (PVE, ablation)
  - It's not what you take out, it is what you leave behind

Surgical Tools: Parenchymal Transections

- All techniques aimed at minimizing blood loss and transfusion need
- Finger crushing
- Crush-clamp technique
- Staplers
- Hydrojet and CUSA
- Aquamantis
- Ligasure, harmonic



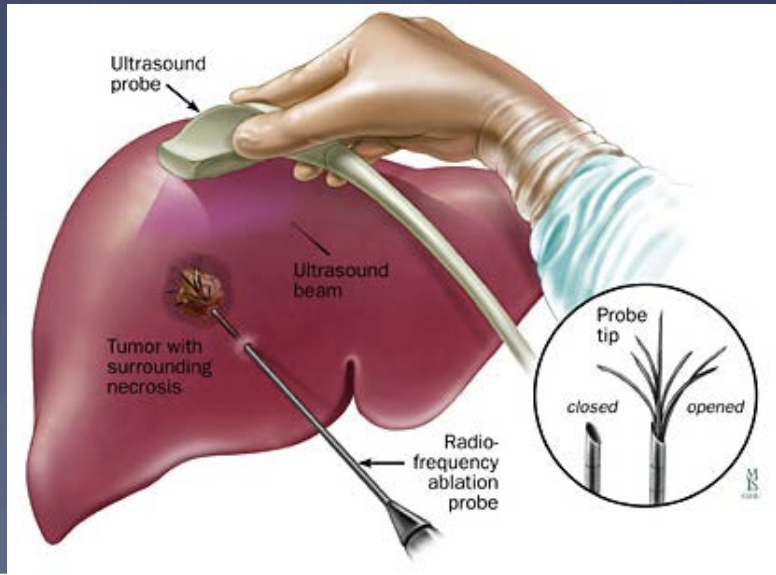
Annals of Surgical Oncology
December 2014, Volume 21, Issue 13, pp 4278–4283

A Retrospective Comparison of Microwave Ablation vs. Radiofrequency Ablation for Colorectal Cancer Hepatic Metastases

Authors | Authors and affiliations

Camilo Correa-Gallego, Yuman Fong, Mithat Gonen, Michael I. D'Angelica, Peter J. Allen, Ronald P. DeMatteo, William R. Jarnagin, T. Peter Kingham

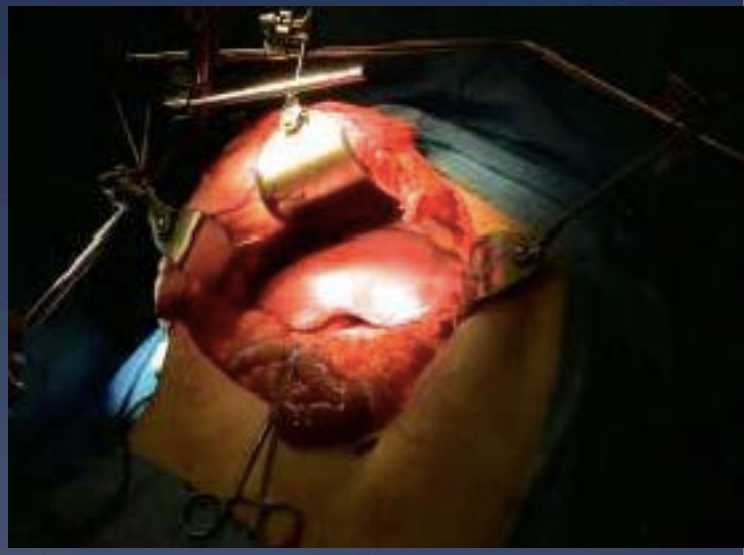
- Combined procedures
- Ablation with resection



Laparoscopic vs. open resections

The morbidity of an open abdomen has been recognized

- Trauma – incisions, exposure, manipulation
- Pain / Narcotics / Ileus / Prolonged recovery
- Fluid shifts / higher transfusion rates
- Immunosuppression
- Physiologic changes associated with an open abdomen

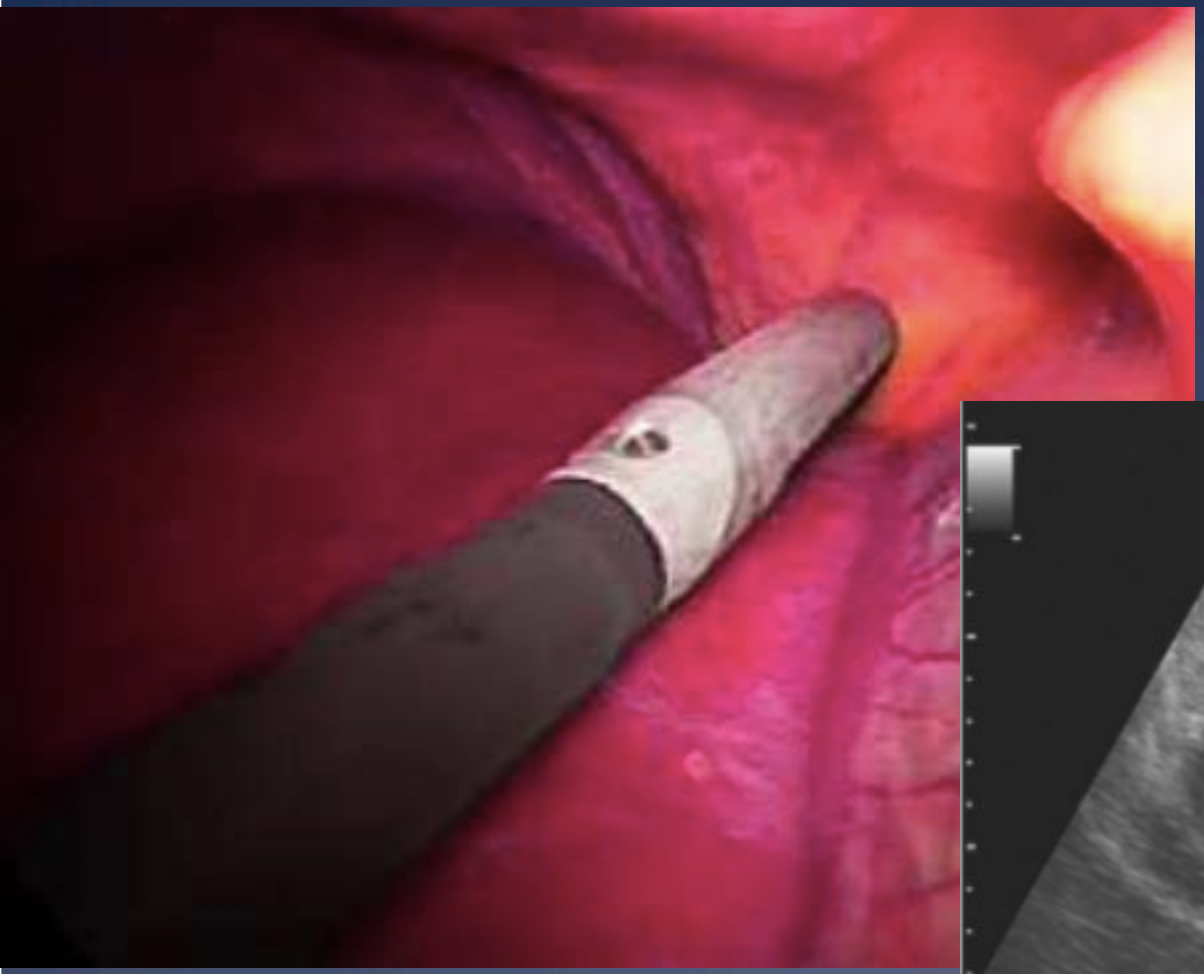


Long term: incisional hernias and bowel obstructions

Select patients in high volume centers to undergo major hepatectomy with equivalent results

Laparoscopic resection for left sided CRLM

Intraoperative ultrasound



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Prometheus, by Paul Rubens

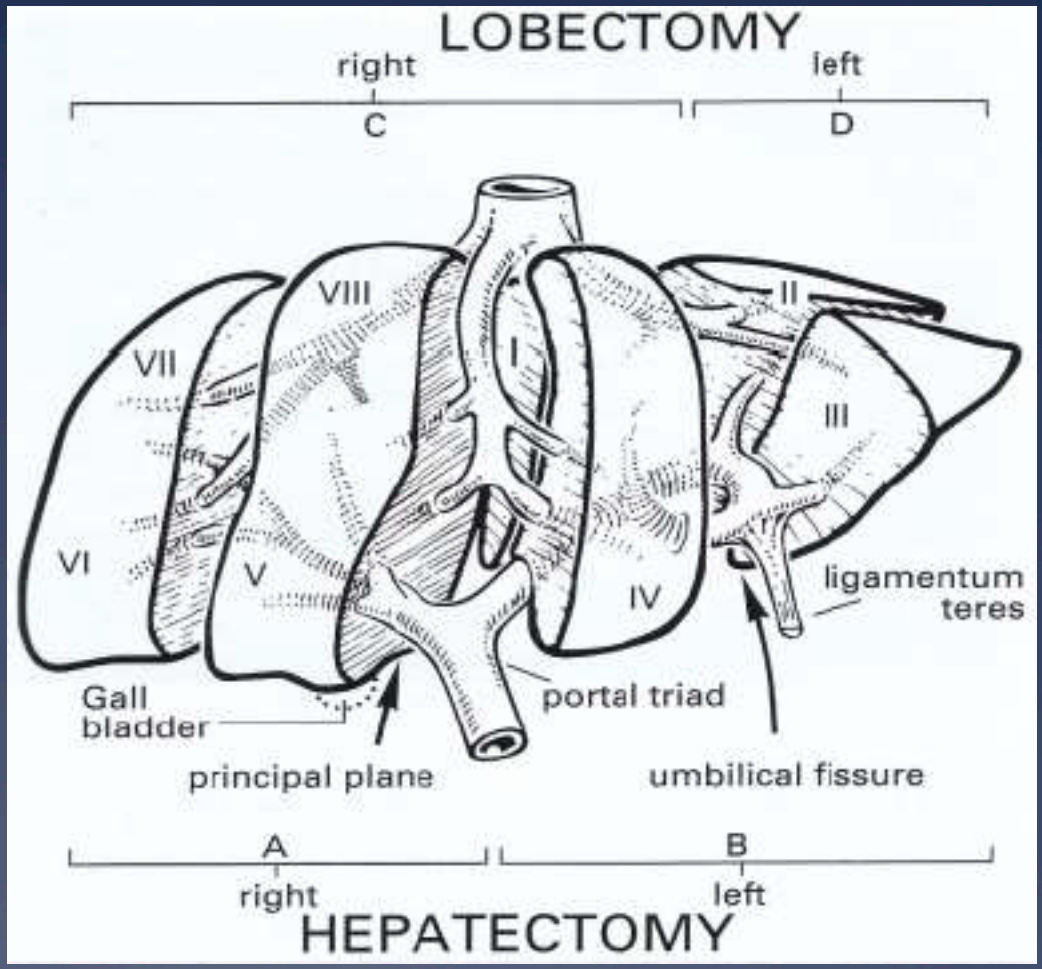
Resectability Criteria

2 Contiguous Segments

Vascularity and Biliary Flow
- Arterial Inflow
- Portal Venous Inflow
- Biliary Outflow
- Hepatic Venous Outflow

Required Remnant Liver
- Normal Liver: > 20%
- Chemo Injury: > 30%
- Cirrhotic Liver: >40%

No Portal HTN
- Plt > 100
- PV gradient < 10



May&Madoff Semin Intervent Radiol 2012;29:81–89

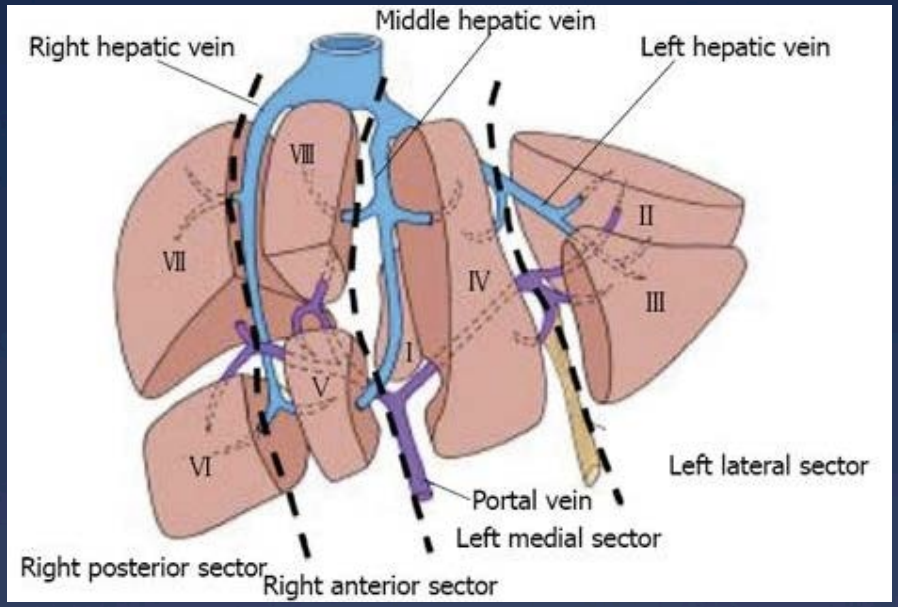
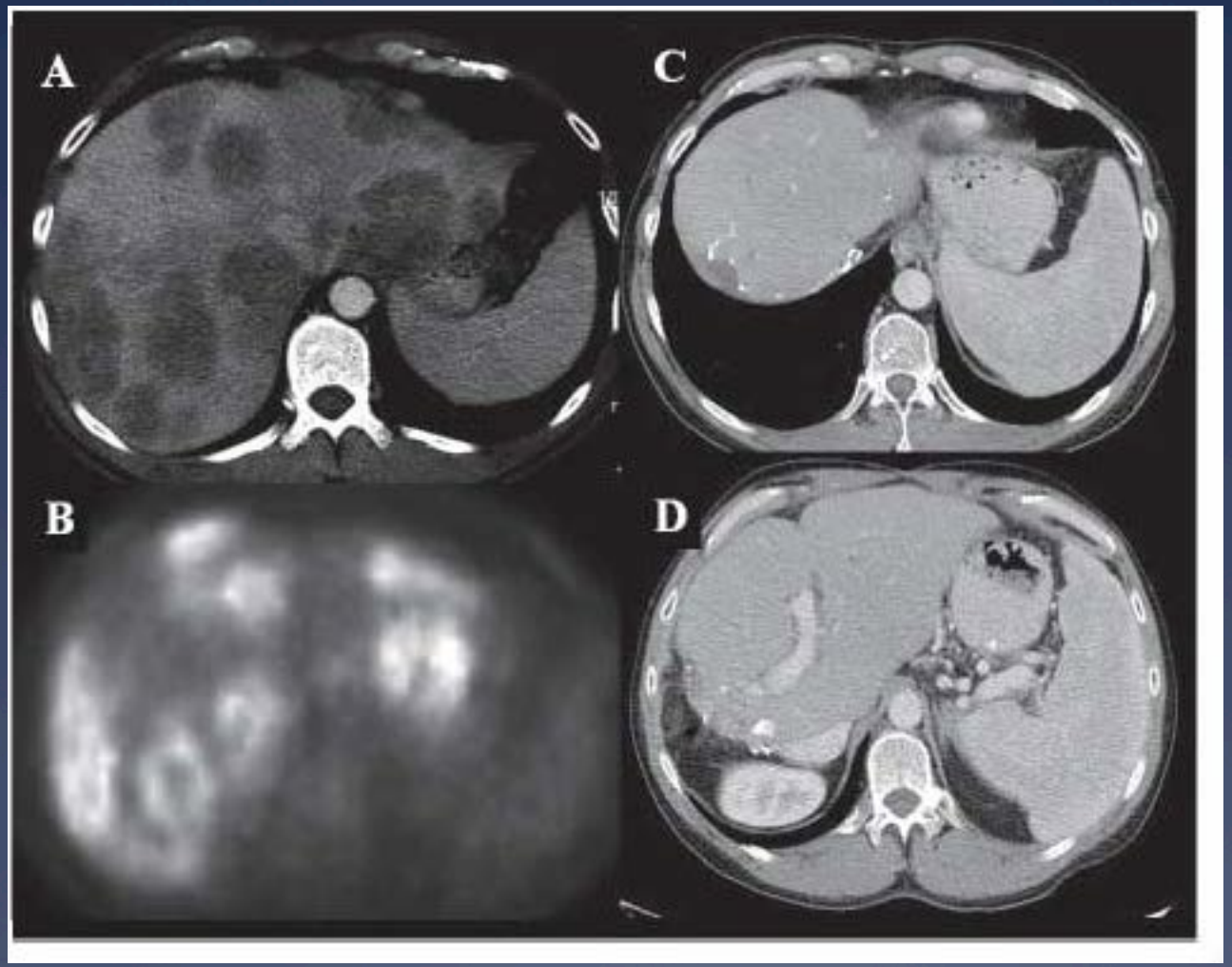


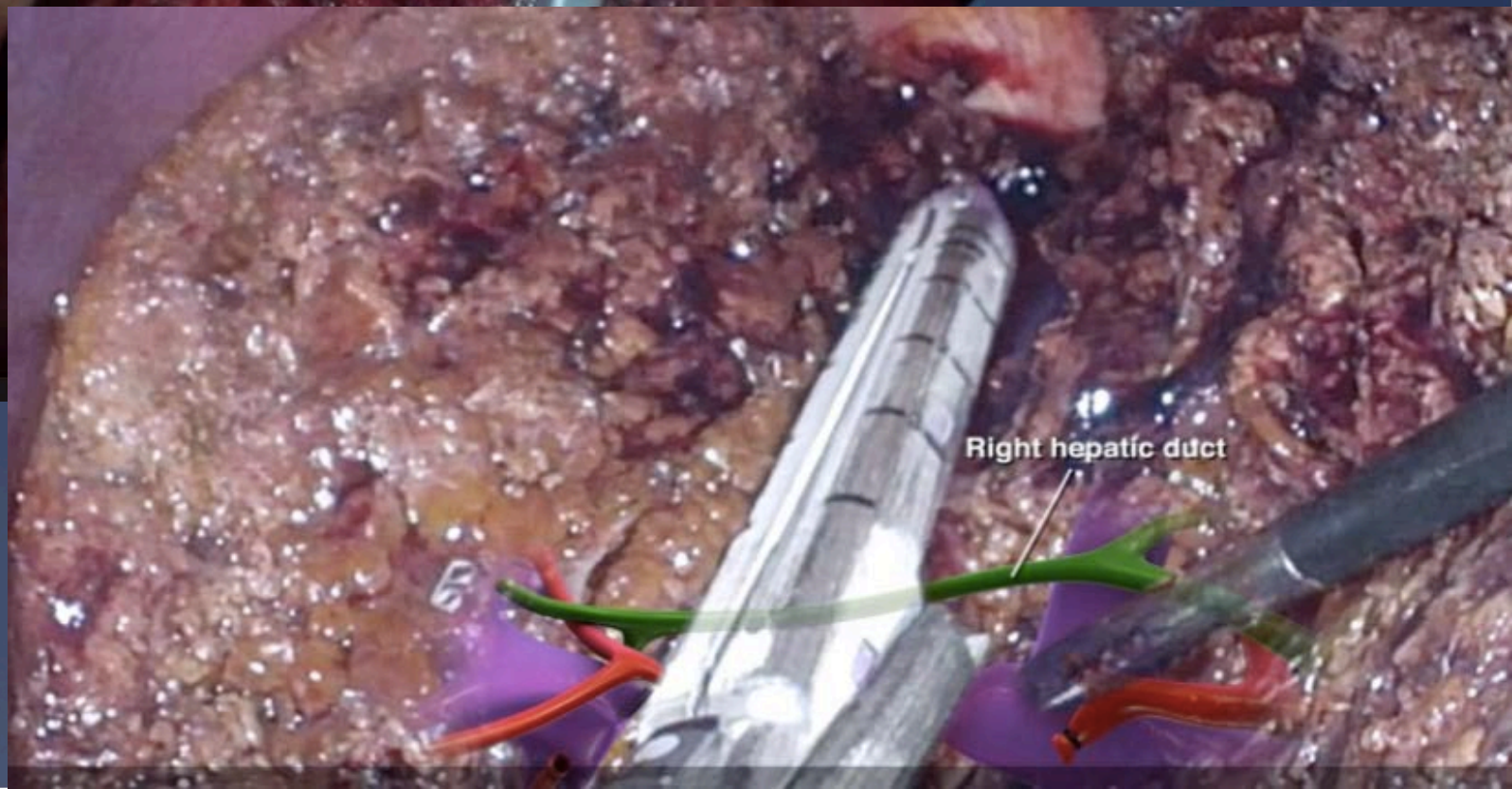
Table 1 Brisbane consensus nomenclature 2000 for describing hepatic resectional surgery based on liver segmental and sectorial anatomy

Anatomical term	Couinaud segments	Term for HRS	Major or minor resection
Right hemi liver	5, 6, 7, 8	Right hemihepatectomy or right hemihepatectomy	Major
Left hemi liver	2, 3, 4 ($^{+/-}$ 1)	Left hemihepatectomy or left hemihepatectomy	Major
Right anterior section	5, 8	Right anterior sectionectomy	Minor
Right posterior section	6, 7	Right posterior sectionectomy	Minor
Left medial section	4	Left medial sectionectomy or resection segment 4 or segmentectomy 4	Minor
Left lateral section	2, 3	Left lateral sectionectomy or bisegmentectomy 2, 3	Minor
-	4, 5, 6, 7, 8 , ($^{+/-}$ 1)	Right trisectionectomy or extended right hemihepatectomy or extended right hepatectomy	Major
-	2, 3, 4, 5, 8 , ($^{+/-}$ 1)	Left trisectionectomy or extended left hemihepatectomy or extended left hepatectomy	Major

"Non-anatomical" resections are also performed either as the main index procedure or in combination with the above anatomical hepatic resectional surgery. A non-anatomical resection refers to a situation in which there is a small tumour that is excised with a negative margin but leaving a remnant segment – a so-called "chip-shot" or metastectomy.

Big surgery: Patients with extensive disease can be treated




Right hepatic duct

Staged Liver Resection

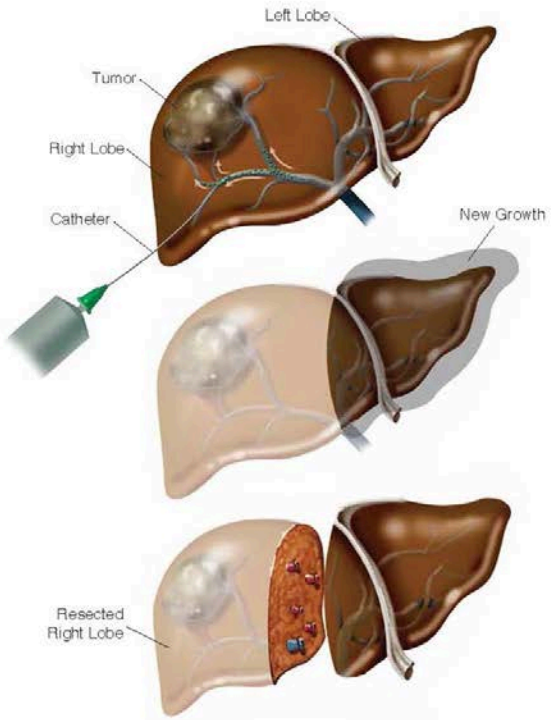


Figure 1. Right portal vein embolization is performed to allow for left liver hypertrophy prior to second-stage right hepatectomy.

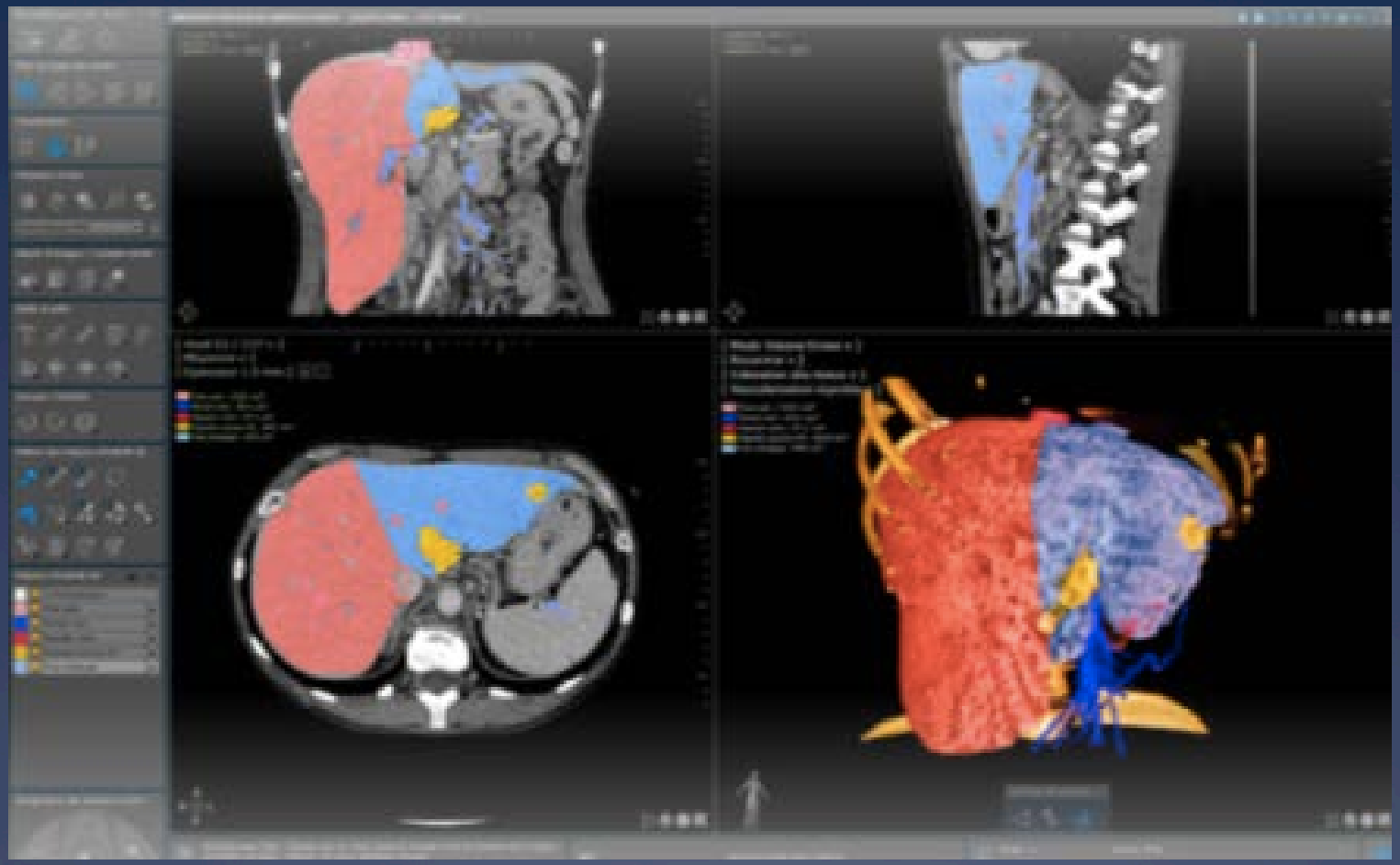
- Extensive bilobar metastases
- Initial resection of lesions in FLR
- PVE to contralateral (more diseased) segment
- Subsequent resection of this embolized segment

- Contraindications to PVE:
  - Ipsilateral thrombus
  - Portal hypertension

https://www.pennmedicine.org/~/media/images/medical%20and%20research%20images/clinical%20briefings%20images/2015_colorectalcancer_livergraphic_1.ashx?la=en

Staged liver resection - tools

- Need for adequate liver remnant (FLR)
  - TELV = -794.41 + 1267.28 (BSA)
- Cross sectional imaging with CT or MRI
- Quantitative assessment with indocyanine green clearance test (ICG) in Far East
- Volumetrics (Pathfinder, Myrian)



Liver resection techniques

Portal vein embolization

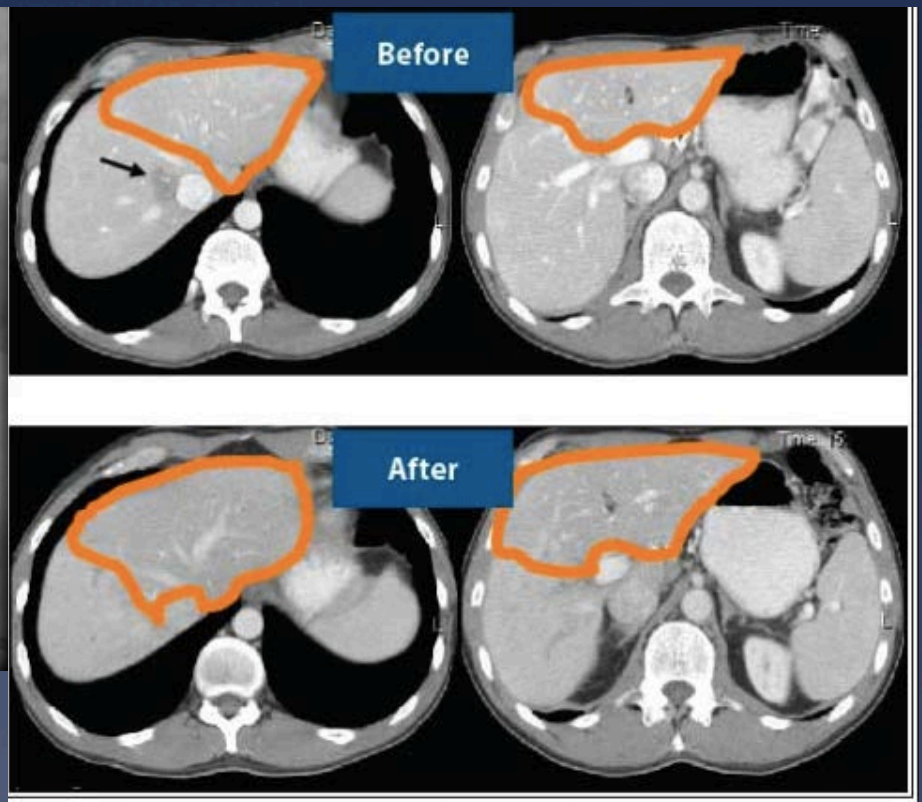


Figure: The Use of Preoperative Portal Vein Embolization to Increase Future Liver Remnant Volume—Although the liver metastasis (arrow) is small, its location adjacent to the vena cava and the right and middle hepatic veins mandates formal right hepatectomy. Volumetry studies are utilized to estimate future liver remnant volume (outlined in orange). Estimated volumes ("Before") were considered inadequate, given prior treatment with chemotherapy; portal vein embolization was performed, successfully increasing future liver remnant volume ("After").

Response to PVE

Normal livers

* regenerate 12 to 21 cm3/day
* sufficient hypertrophy typically occurs within 2 to 4 weeks

Cirrhotic patients:

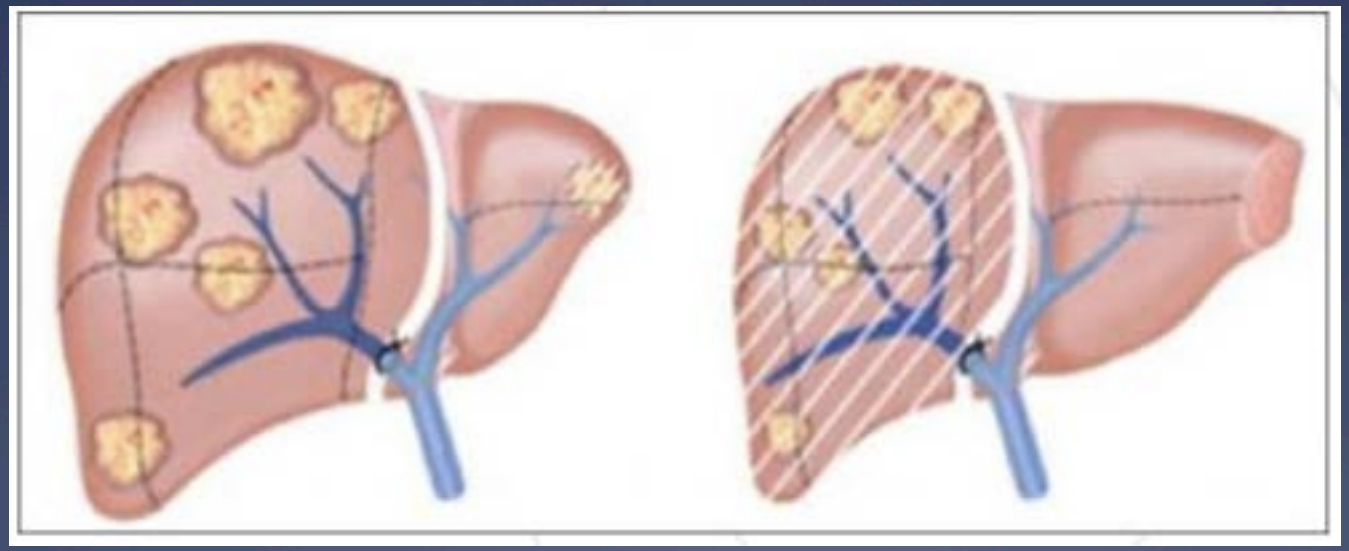
* 9 cm3/day
* Sufficient hypertrophy in 4-6 wks

PVE complications

- General: subscapular hematoma, hemobilia,hemoperitoneum, vascular injuries, pneumothorax, and cholangitis.
- specific to PVE: nontarget embolization, recanalization of embolized segments, and complete PVT

ALPPS Procedure

- **Associating Liver Partition and Portal vein Ligation for Staged hepatectomy**
  - **controversial**



Simultaneous resection of primary and CRLM

- Still controversial, no trials
- Considerations:
  - Similar or decreased complication rate (several series) with simultaneous
  - patients who underwent simultaneous resection maybe would have progressed to unresectabilty during the interval between removal of the primary and metastasectomy.
  - 2/3 patients can be **spared unnecessary hepatic resection** by using a delayed-resection approach

Simultaneous resection

Perform a simultaneous resection:

- in patients with low-volume disease in the liver
- when the risk of early and rapid progressive disease is relatively low.

Avoid simultaneous resection:

- in patients who appear frail
- When liver disease is best addressed in a delayed fashion
  - such as with obstruction or bleeding.

Work up prior to referral

Basic work up of a suspected liver metastasis

HP

* Patient's fitness for surgery

Biochemical tests:

* CBC, CEA level, liver panel

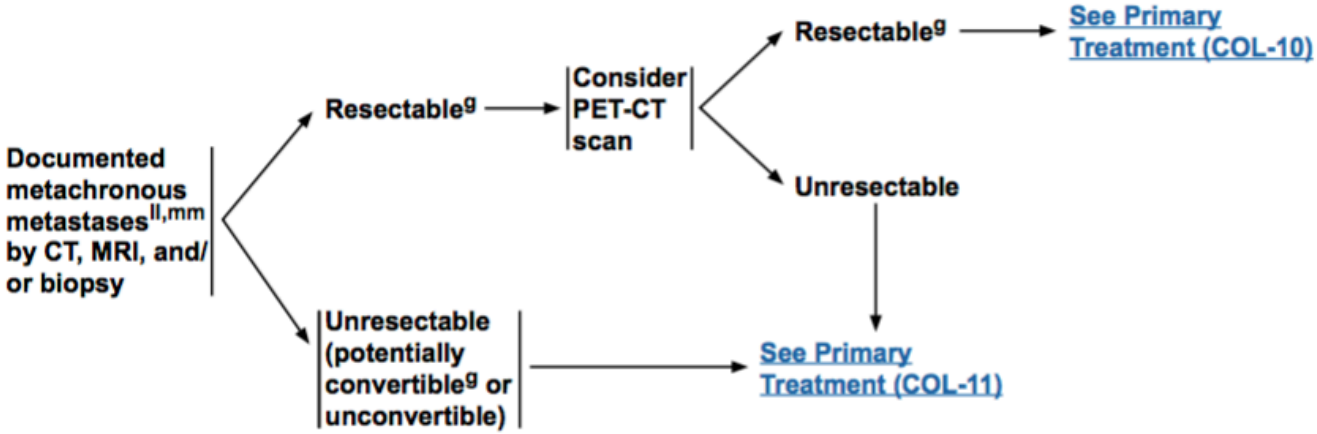
Imaging:

* CT chest/abdo/pelvis
* CT liver to be 3 phasic

Staging laparoscopy:

* Reserve for patients with high CRS (poor prognostic profile)

Metachronous CRLM NCCN 2016

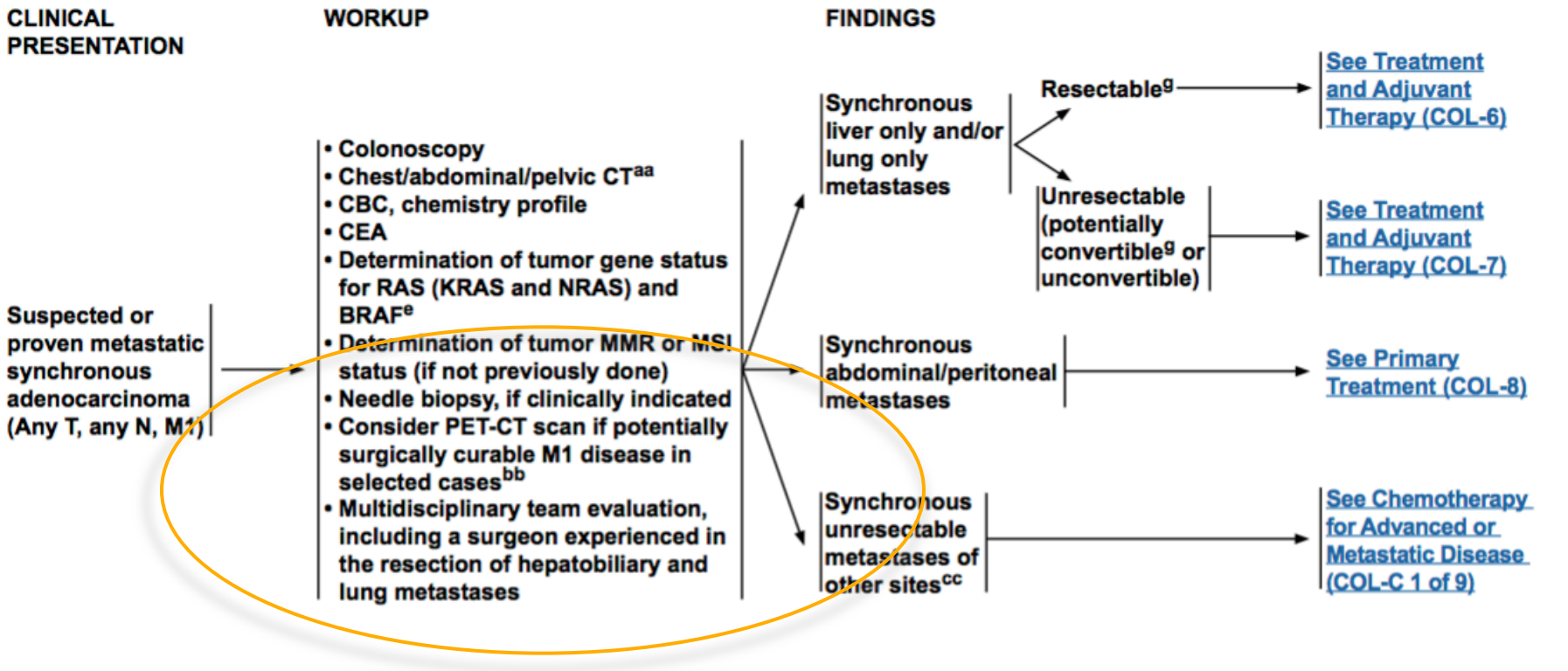


[g]See Principles of Surgery (COL-B 2 of 3).

[ll]Determination of tumor gene status for RAS (KRAS and NRAS) and BRAF. Determination of tumor MMR or MSI status (if not previously done). See Principles of Pathologic Review (COL-A 4 of 5) - *KRAS*, *NRAS* and *BRAF* Mutation Testing and Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing.

[mm]Patients should be evaluated by a multidisciplinary team including surgical consultation for potentially resectable patients.

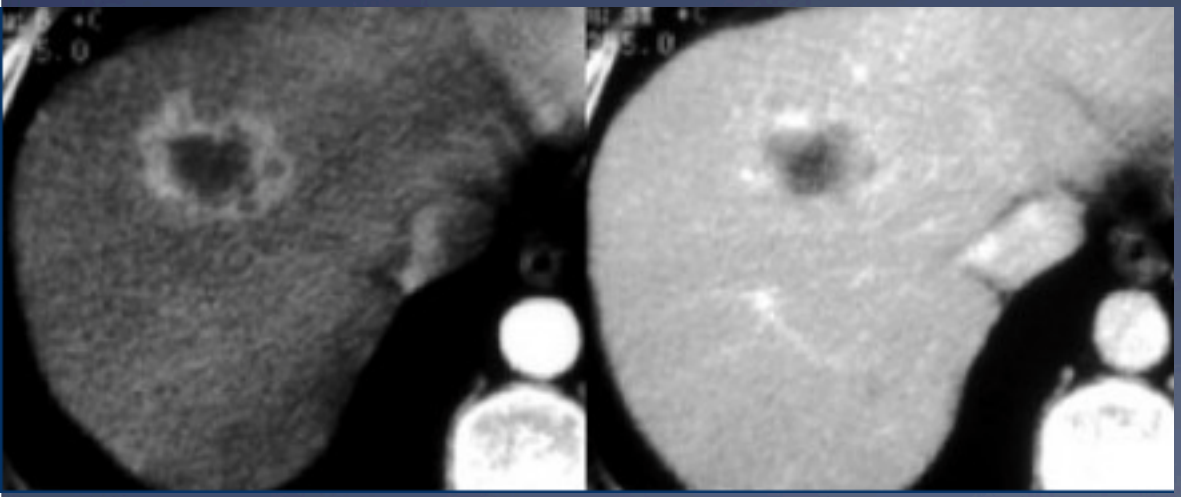
Synchronous CRLM, NCCN 2016



[e] See Principles of Pathologic Review (COL-A 4 of 5) - KRAS, NRAS and BRAF Mutation Testing and Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing.
[g] See Principles of Surgery (COL-B 2 of 3).
[aa] CT should be with IV contrast. Consider MRI with IV contrast if CT is inadequate.
[bb] Moulton CA, Gu CS, Law CH, et al. Effect of PET before liver resection on surgical management for colorectal adenocarcinoma metastases: a randomized clinical trial. JAMA 2014;311:1863-1869.
[cc] Consider colon resection only if imminent risk of obstruction or significant bleeding.

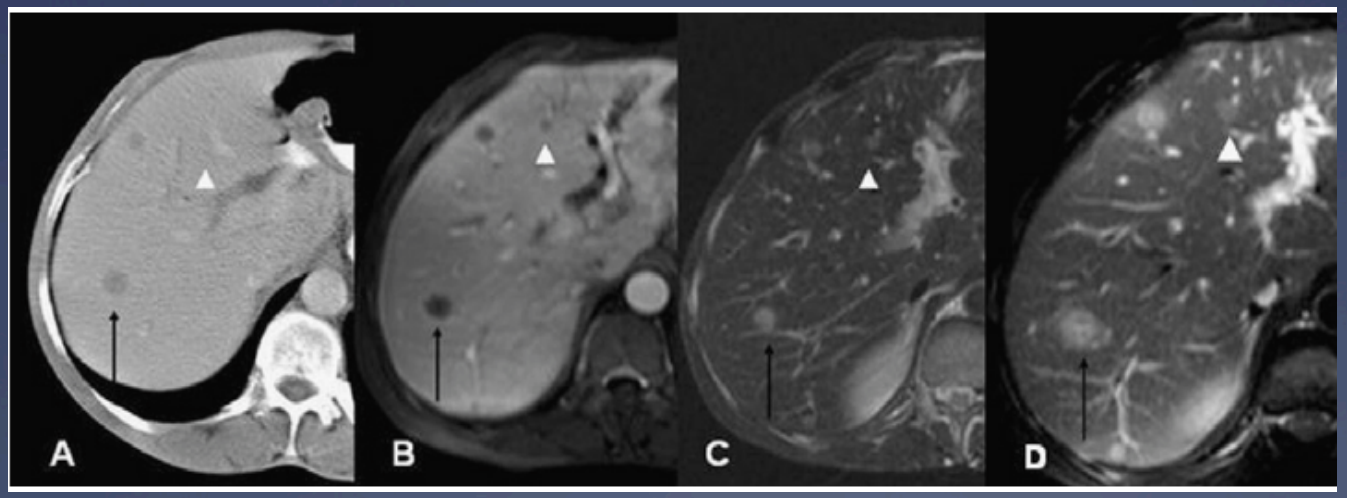
CT scan chest/abdo/pelvis

- Standard CT should be 3 phasic with arterial, portal venous, and delayed phases
- Portal venous phase is important, because the lesions are not typically well vascularized.
- Arterial phase -? CRLM vs. hemangiomas, or to better define the arterial anatomy of the liver.



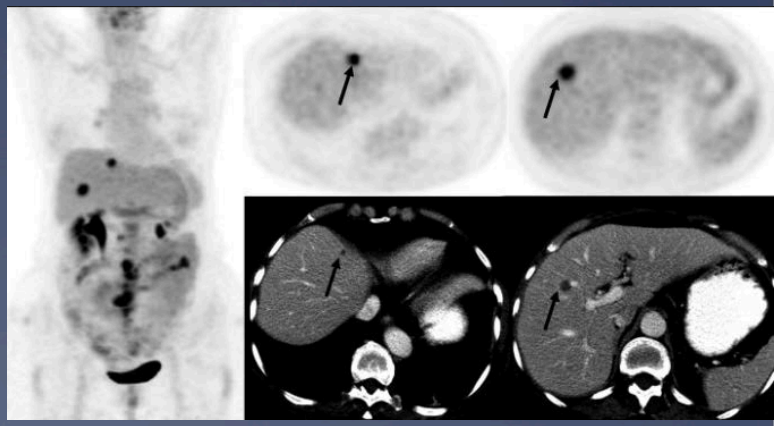
MRI

- MRI is most useful to evaluate indeterminate hepatic lesions
- To define the relationship of tumors to the hepatic vasculature and biliary tree using MRCP
- Not used routinely



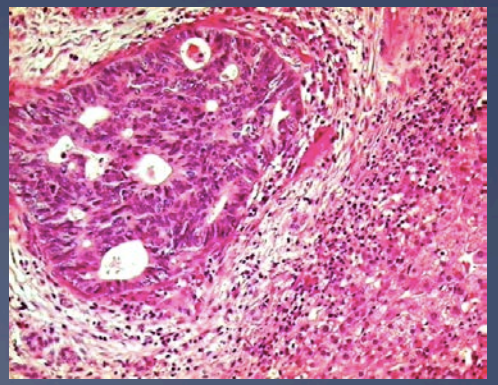
PET CT

- Consider PET-CT scan if potentially surgically curable M1 disease in selected cases (Moulton et al 2014)
- Uses IV radioactive tracer, which in most cases is ^{18}F-FDG.
  - Tracer cannot proceed down the glycolytic pathway → accumulates within glucose-avid cancer cells.
- Limitations:
  - poor sensitivity for lesions <1 cm
  - larger lesions are not FDG avid
  - Anatomic detail low
  - FPs :
    - Inflammation
    - Infection
  - FNs: Recent chemotherapy

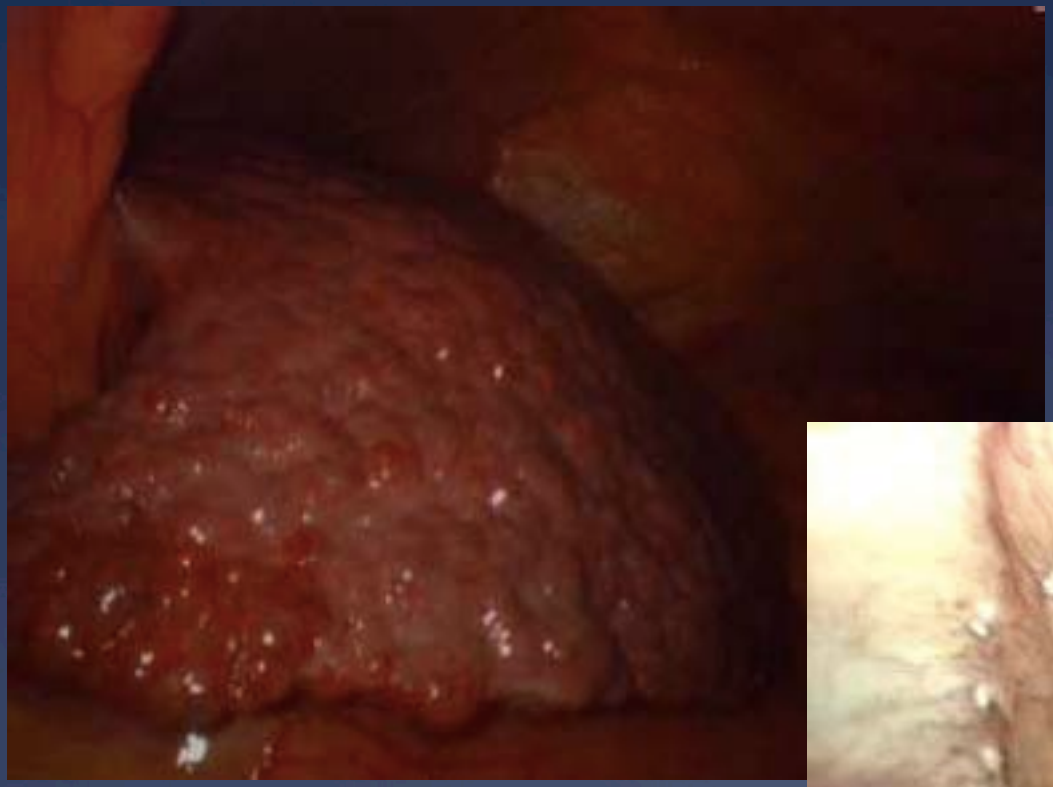


Role of liver biopsy

- only indicated to confirm the diagnosis when the clinical picture is unclear. (after CT and MRI unclear)
- differentiation between metastatic tumors and benign hepatic lesions can usually be done with imaging
- If done → core biopsy preferable
- The risk of tract seeding low
  - with only a few case reports in the literature.

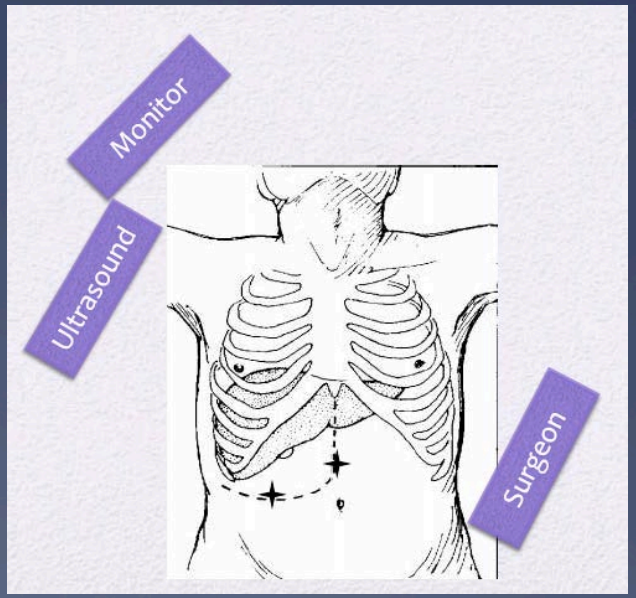


Staging laparoscopy



Staging laparoscopy

- Select cases:
  - Preexisting liver disease
  - Asictes, suspicion of carcinomatosis
  - High CRS score
    - Advanced primary
    - LN involved
    - High burden disease
    - Synchronous



Management of post hepatectomy complications

Post hepatectomy outcomes

The mortality due to resection CRLM decreased significantly over the past 3 decades

- less than 10% across major series

Morbidity:

- largely due to metabolic and immunologic derangements
- in most series is over 20%
- Liver insufficiency and liver failure
  - most dangerous liver-related complication
  - in 3% to 8% of major hepatic resections

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Original Study

Surgical and Oncologic Outcomes After Major Liver Surgery and Extended Hemihepatectomy for Colorectal Liver Metastases

Inge Ubink, Jennifer M.J. Jongen, Maarten W. Nijkamp, Eelco F.J. Meijer, Thomas T. Vellinga, Richard van Hillegersberg, I. Quintus Molenaar, Inne H.M. Borel Rinkes, Jeroen Hagendoorn

- 117 patients underwent major liver surgery at a Dutch tertiary referral center 2000-2015
- Ninety-day mortality 8%.
- Major postoperative complications in 27% of patients
- DFS 11mos
- Median OS 44mos

Post CRLM resection mortality

Study	No. Patients	Operative Mortality (%)	SURVIVAL (%)			
			1-Year	3-Year	5-Year	10-Year
Schlag, 1992	122	4	85	40	30	—
Doci et al, 1991	100	5	—	28	—	28
Younes et al, 1991	133	—	91	—	—	—
Rosen et al, 1992	280	4	84	47	25	—
Scheele et al, 1995	434	4	85	45	33	20
Nordlinger et al, 1996	1568	2.3	88	64	28	
Jamison et al, 1997	280	4	84	—	27	20
Fong et al, 1999	1001	2.8	89	57	36	22
Minagawa et al, 2000	235	0.85	—	51	38	26
Choti et al, 2002	226	1	93	57	40	26
Belli et al, 2002	181	—	91.2	55.3	39.8	—

Post op morbidity

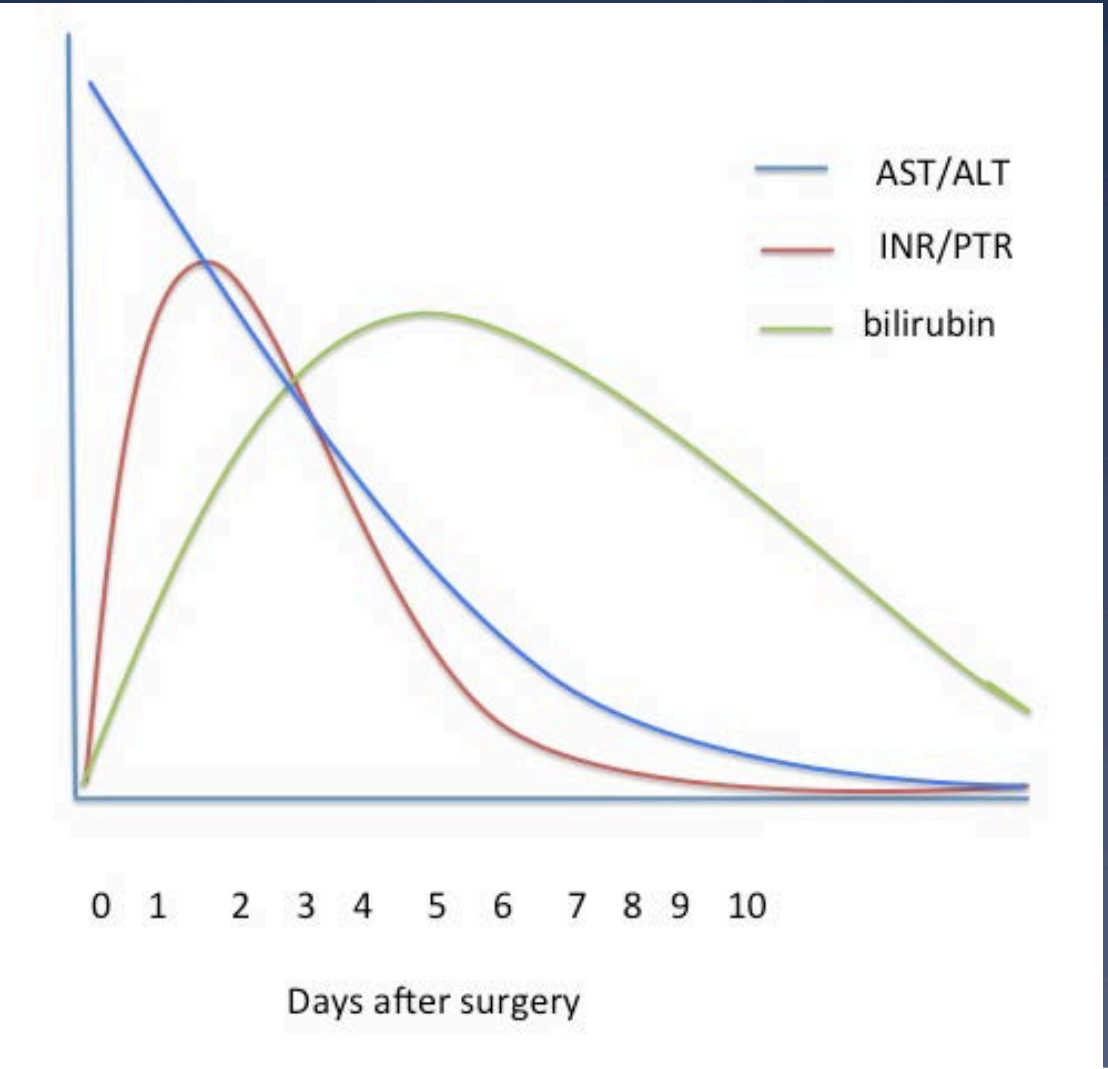
	Scheele et al, 1990 (%)	Schlag et al, 1990 (%)	Doci et al, 1991	Fortner et al, 1984 (%)	Nordlinger et al, 1987 (%)	Coelho et al, 2004	Mala et al, 2002 (%)	Jarnagin et al, 2002	Cady et al, 1998
Total resections	219	122	100	75	80	83	146	1803	244
Liver related									
Hemorrhage	7 (3)		3	1 (1)	1 (1)		4 (3)	18	1
Bile fistula	8 (4)	5 (4)	4			11	2 (1)		2
Perihepatic abscess	4 (2)	11 (9)	5	5 (7)	2 (3)			110	1
Liver failure	17 (8)		3	3 (4)	1 (1)	6		99	1
Renal failure	3 (1)		1						
Portal vein thrombosis				1 (1)		1	1 (<1)	9	
General									
GI bleed						5		21	0
DVT	2 (1)			1 (1)				24	<1
Pulmonary embolism	4 (2)			1 (1)	1 (1)				<1
Cardiac/MI	2 (1)	6 (5)	1	1 (1)	1 (1)	1	1 (<1)	21	3
Pneumonia		10 (8)	22	3 (4)		7	13 (9)	54	1
Pleural effusion				6 (8)	3 (4)	11		154	2

- High complication rate does not always translate into a prolonged hospital stay.
- If recognized and treated promptly, most complications do not result in a poor outcome.

Post Operative Care

- Drains – no studies, plan for care and removal needed
- Electrolytes – in setting of cirrhosis, colloids or albumin are preferred to crystalloids
  - Na restriction, judicious diuresis also important
- Hypo/hyperglycemia, hypocalcemia, hypophosphatemia
- Thromboprophylaxis: more hypercoagulable despite high INR/PTT

Normal post op changes in liver enzymes



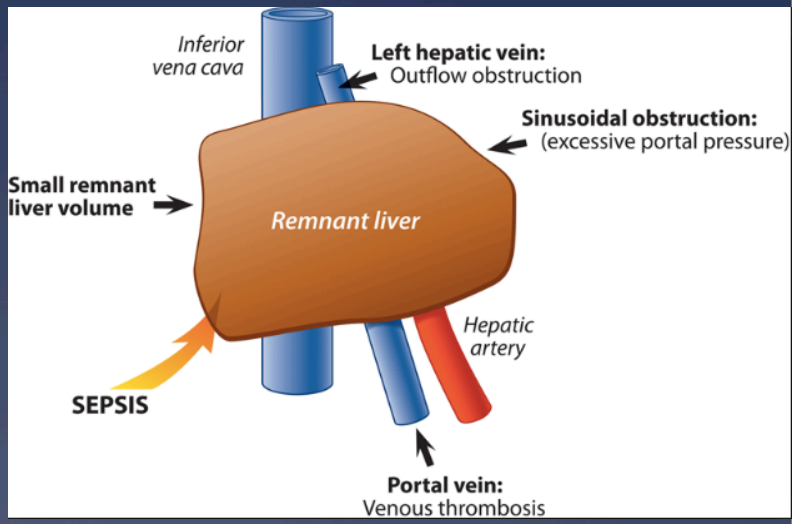
Post operative hepatic failure

- Impaired ability of the liver to maintain synthetic, excretory, and detoxifying functions, >POD4
  - **Prolonged** elevated INR, bili, ascites, encephalopathy
- Risk factors: bleeding, PVT, poorly functioning liver remnant, previous chemo, steatosis, sepsis

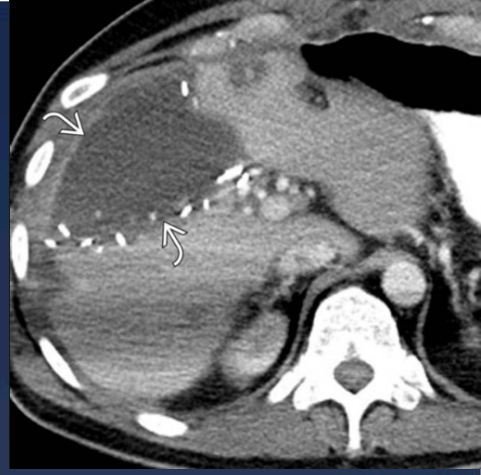
Post operative liver failure management

Largely supportive:

- Support synthetic function with FFP
- Administer colloids – albumin
- Avoid Na administration
- Lactulose for encephalopathy
- Prophylactic antibiotics
- Judicial use of diuretics
- Anticipate and manage HRS
- Image liver (other causes of jaundice?)



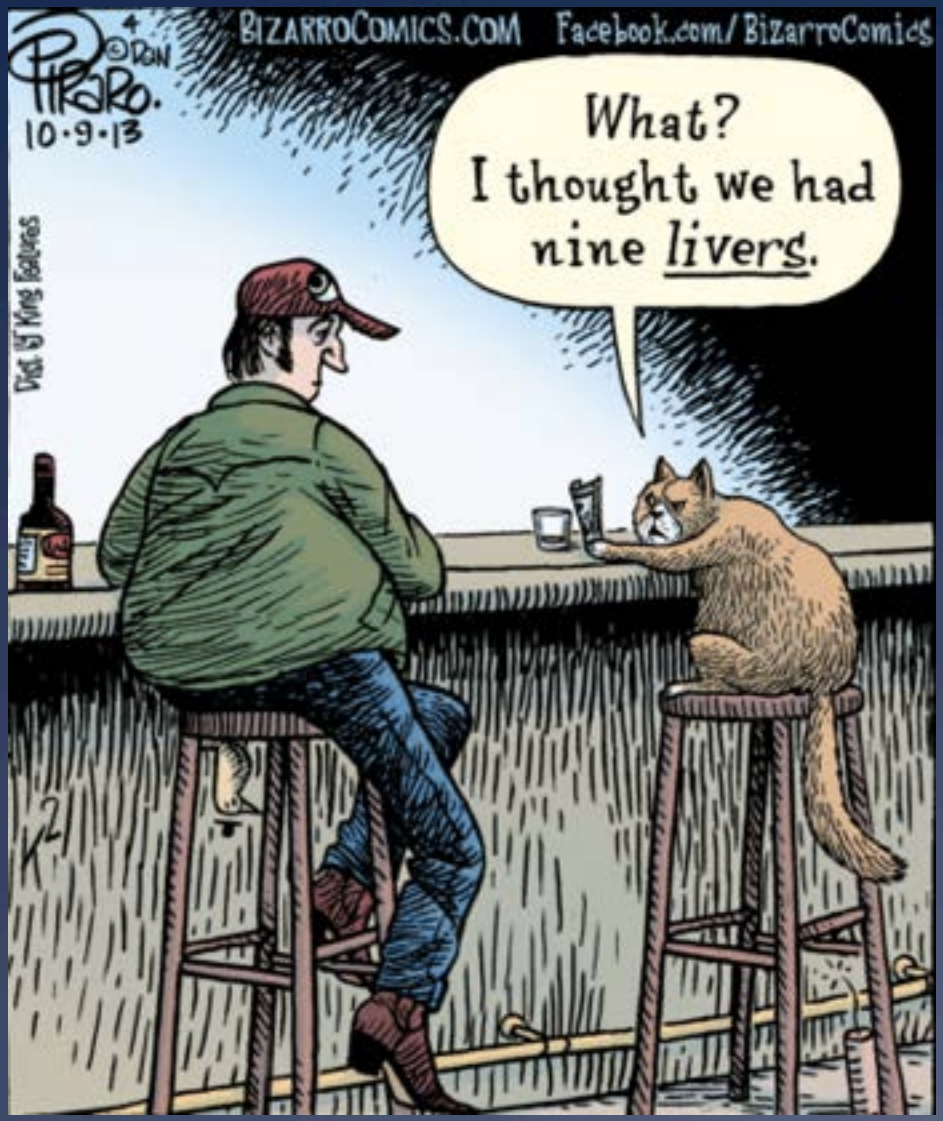
Bile leaks



- 4.8-7.6% in large series
- ISGLS definition = drain fluid bilirubin >3 times serum after POD 3
- Treat associated infection
- Define location and extent
- Drain, ERCP/PTC and consider reconstructive surgery later

Conclusion

- Surgery for CRLM has better outcomes and can cure a small portion of patients
- More extended resections are routine
- Work up should include staging CT abdo/chest and 3-phases, tumor markers
- Prior to referral if possible:
  - Staging CT chest/abdo/pelvis, multiphasic CT liver
  - Laparoscopy, MRI/PET in select patients
- Biopsy for lesions that are indeterminate on at least 2 imaging modalities
- Refer to HPB center early



Thank you

Questions?

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