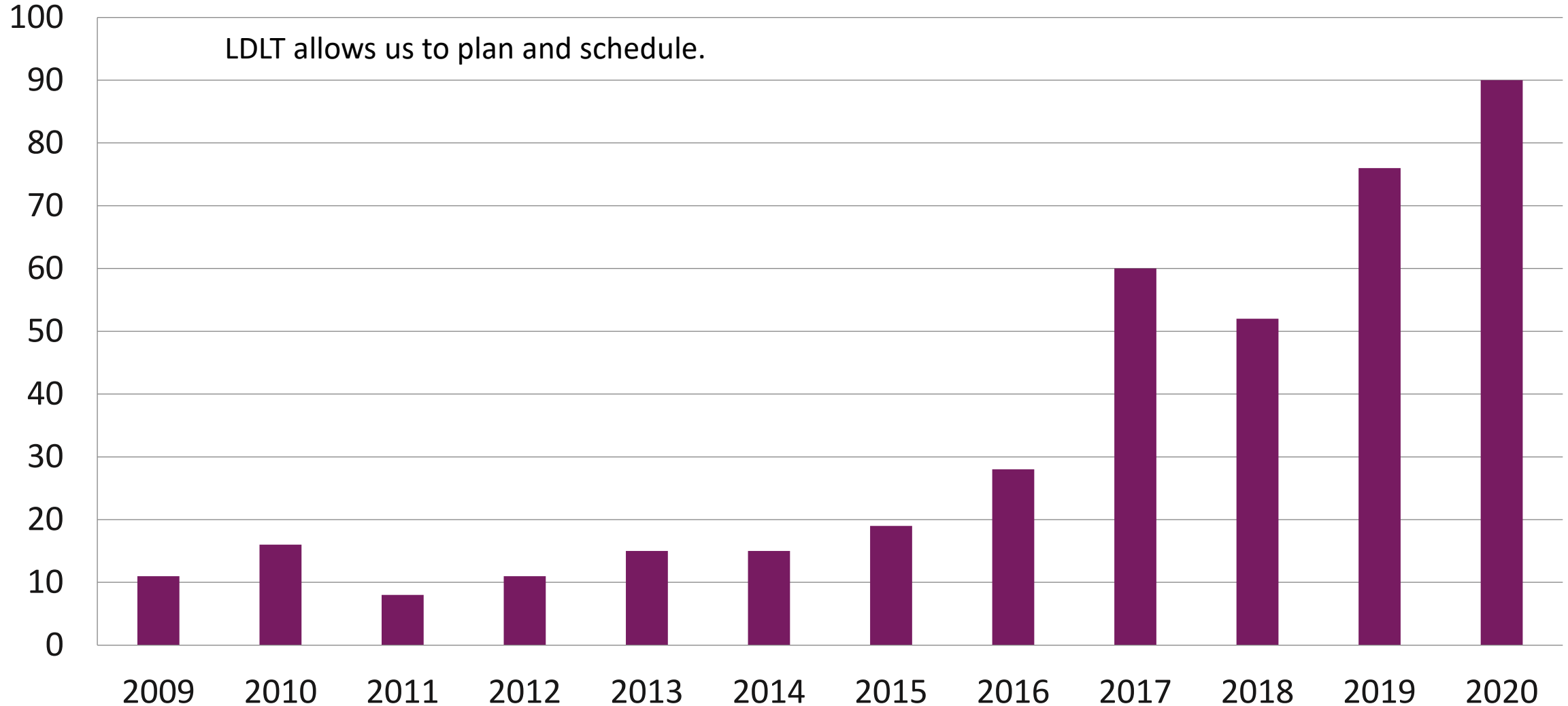


# Living-Donor Liver Transplantation For Patients with Advanced Cancers: Cholangiocarcinoma and Colorectal Metastasis

Christopher B. Hughes, MD  
I have no disclosures.

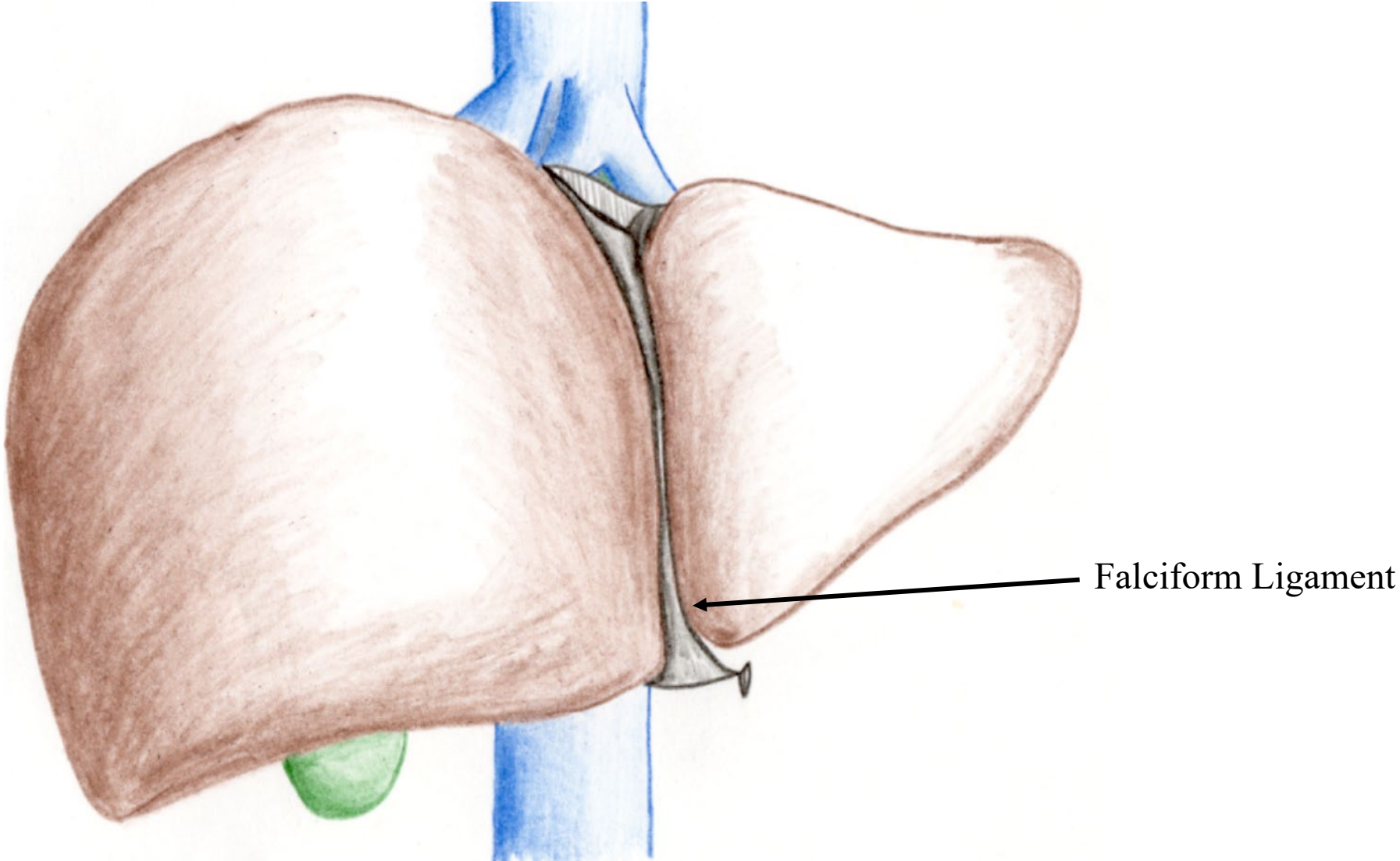


Center	DDLT	LDLT	Total Transplants
Mayo Clinic Arizona	186	1	187
Ochsner Clinic, New Orleans	183	0	183
UCSF	152	21	173
UPMC	66	100	166
UCLA	157	0	157
Tampa General	152	0	152
Indiana	151	0	151
Ohio State	147	1	148
Mayo Clinic Florida	142	0	142
Cincinnati	139	0	139

Good results allow us to take on high-risk cases.

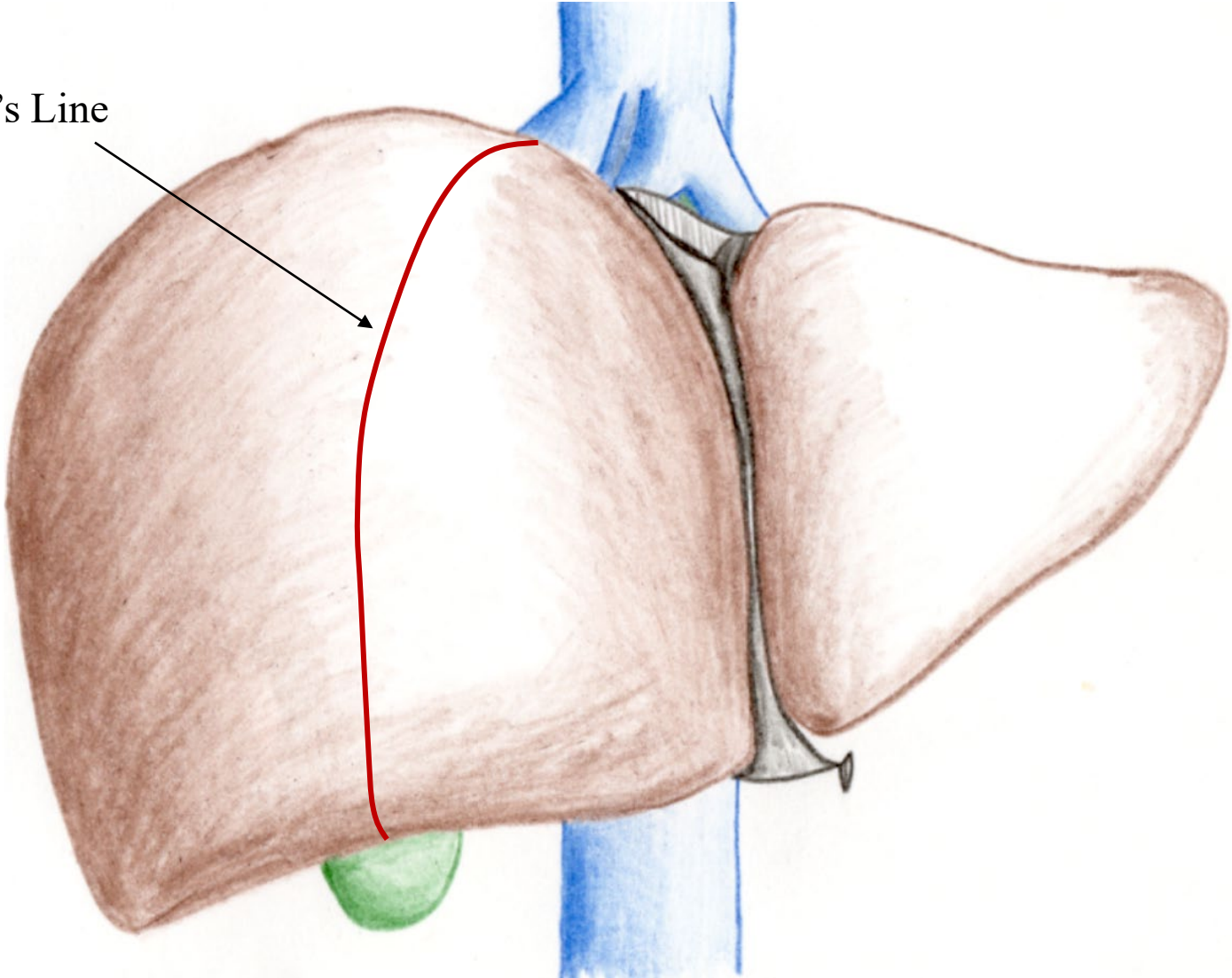
	<b>1-yr PATIENT SURVIVAL (%)</b>
OBSERVED	94.3
EXPECTED	92.8
NATIONAL	92.1

# Liver Anatomy

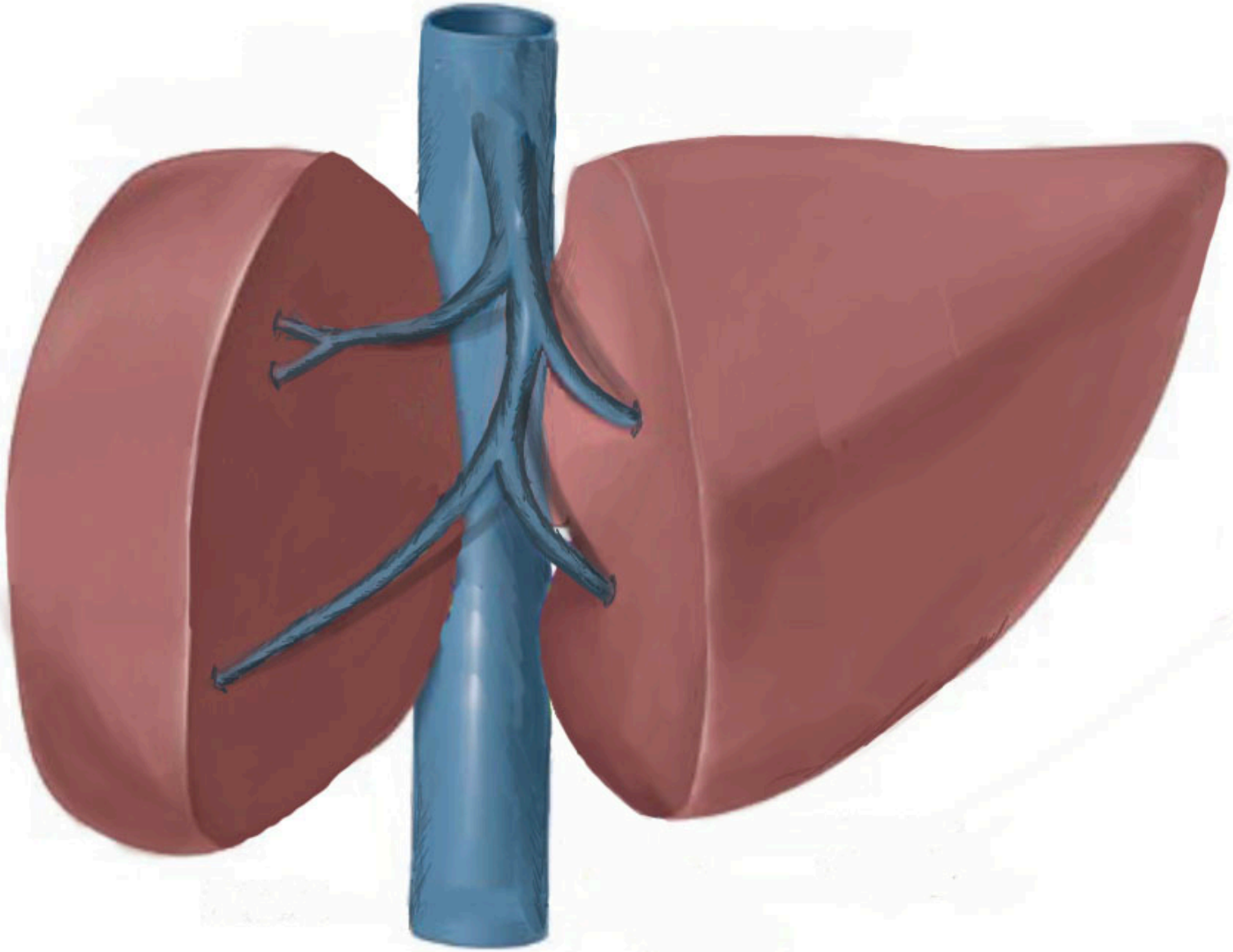


# Liver Anatomy

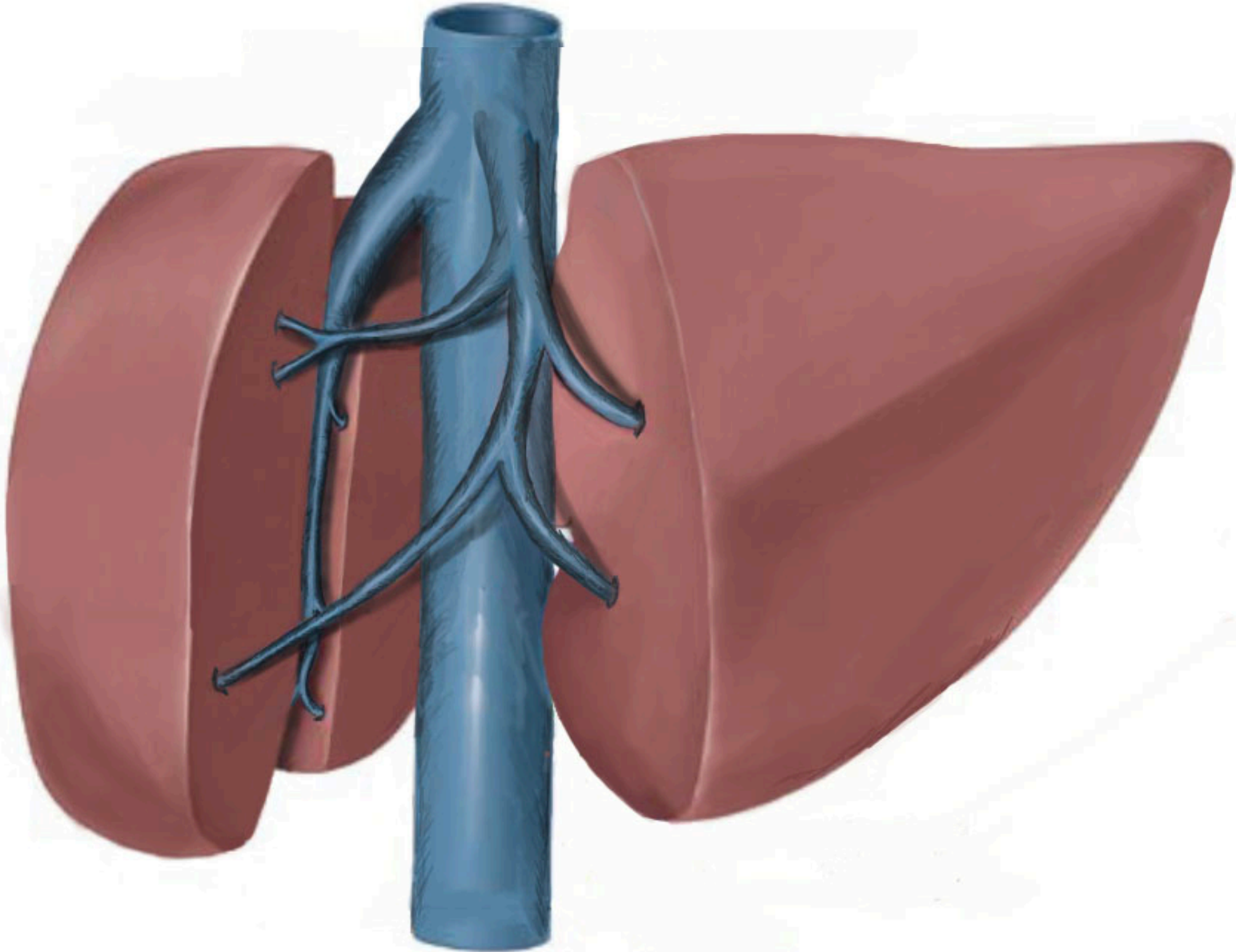
Cantlie's Line



Liver Anatomy—Middle Hepatic Vein

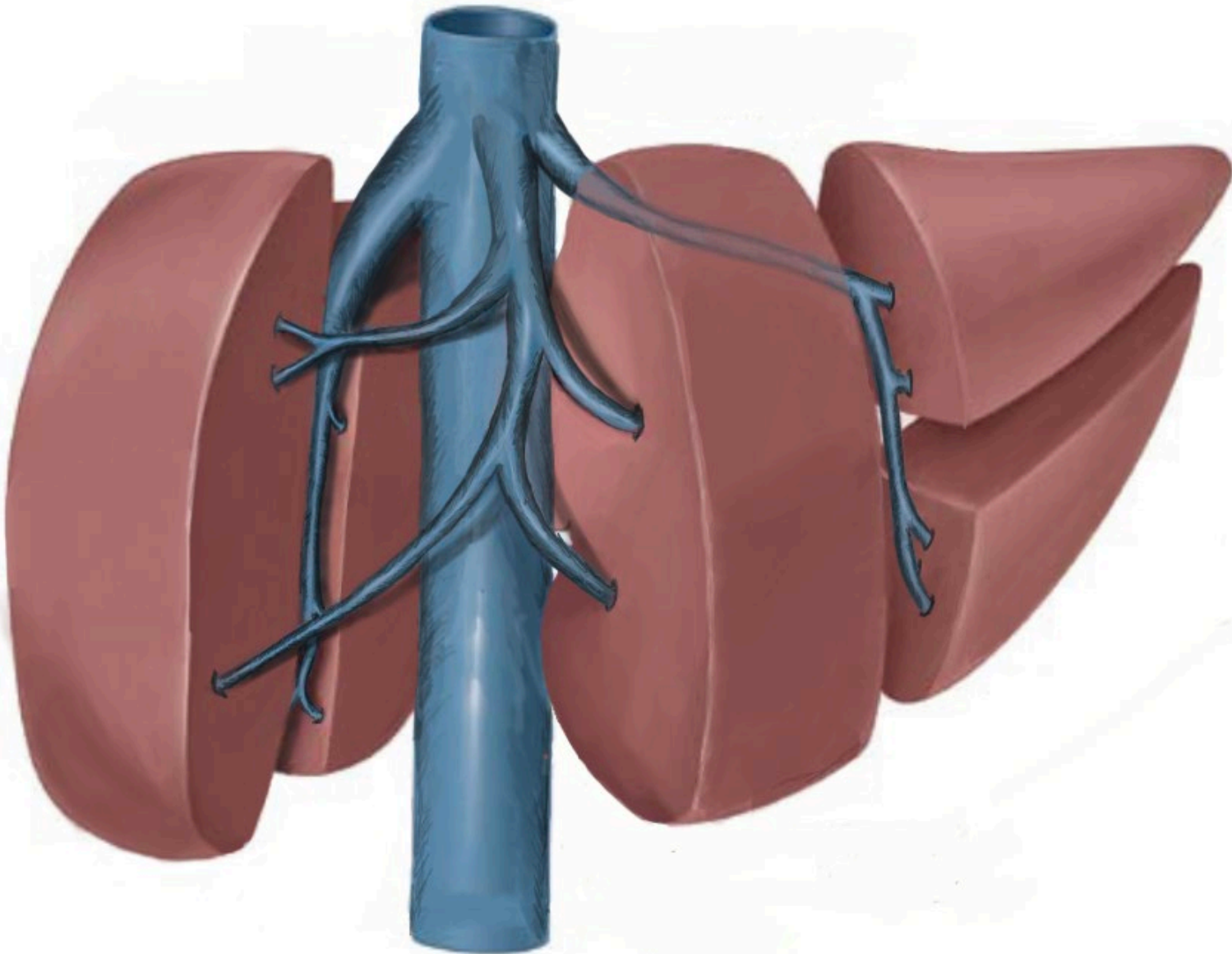


Liver Anatomy—Middle and Right Hepatic Veins

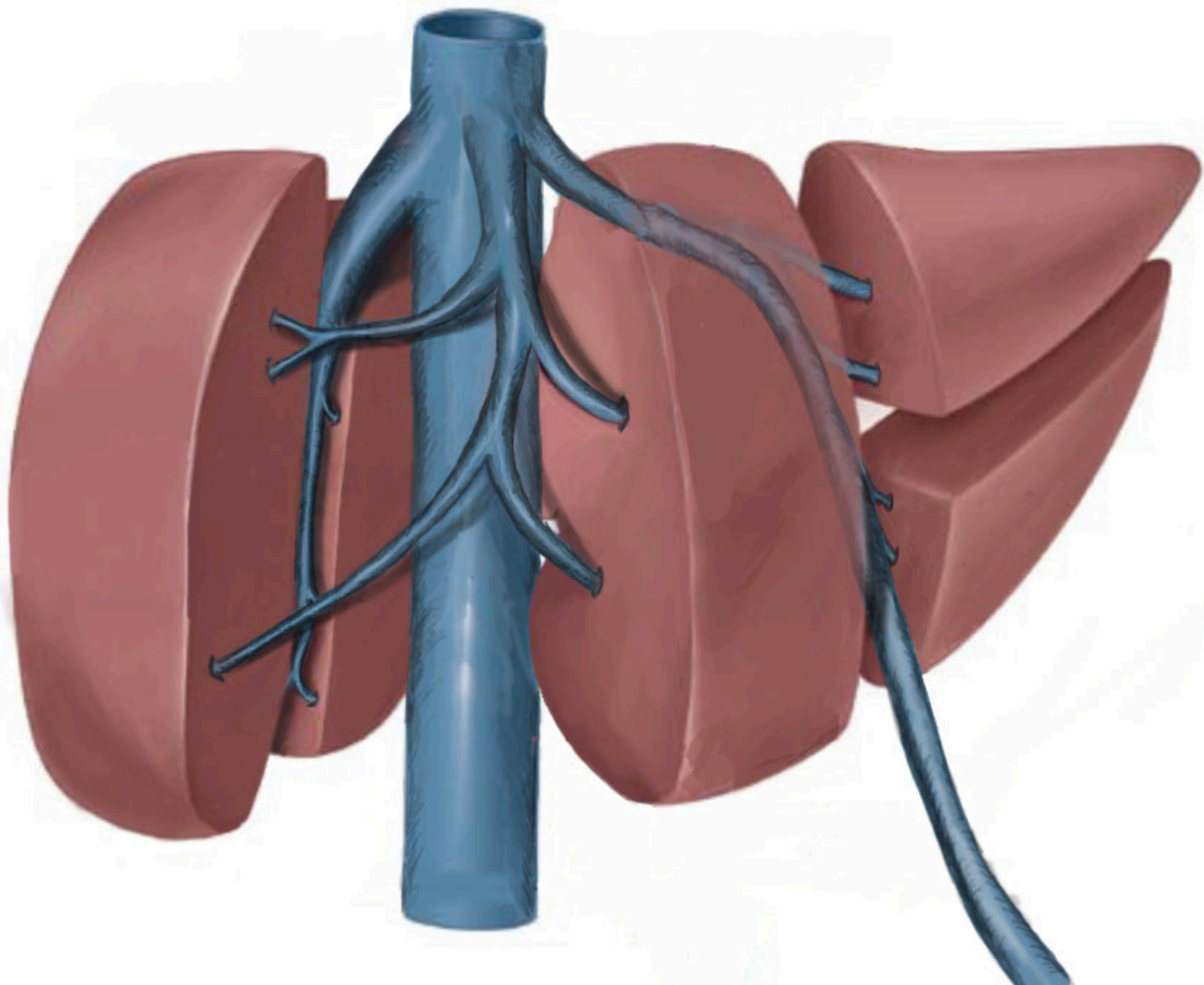




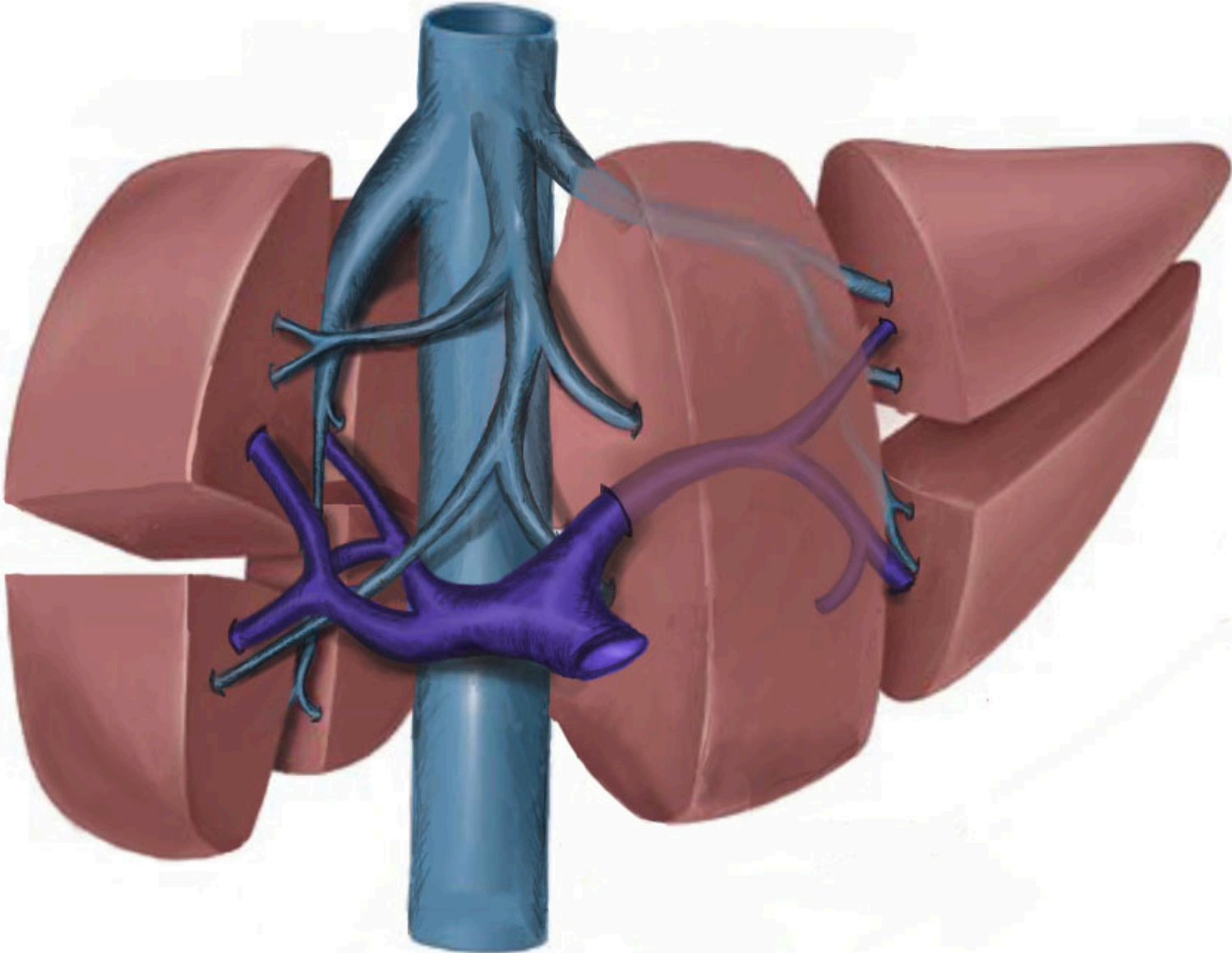
Liver Anatomy—Middle, Right, and Left Hepatic Veins



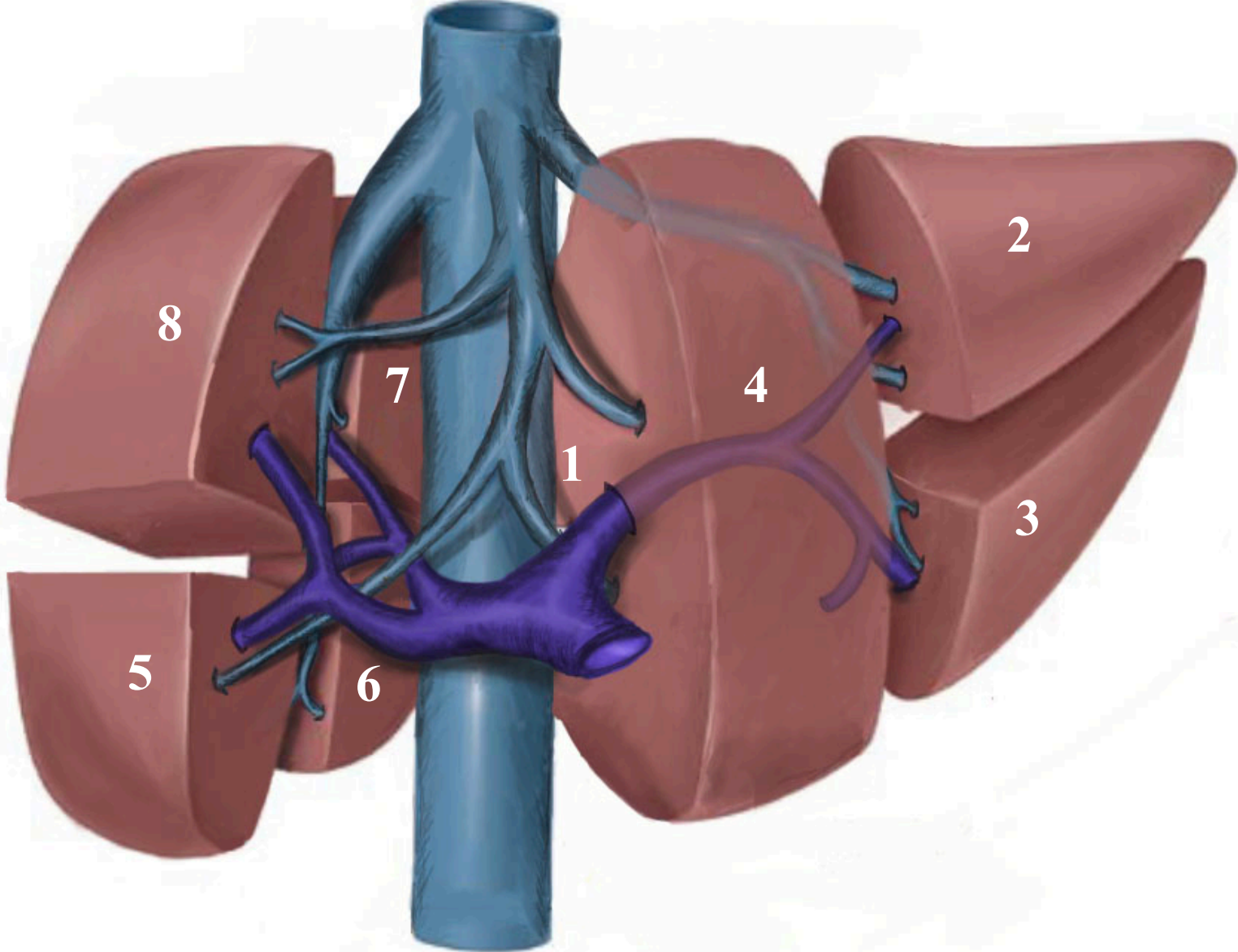
Liver Anatomy—Middle, Right, and Left Hepatic Veins and Umbilical Vein



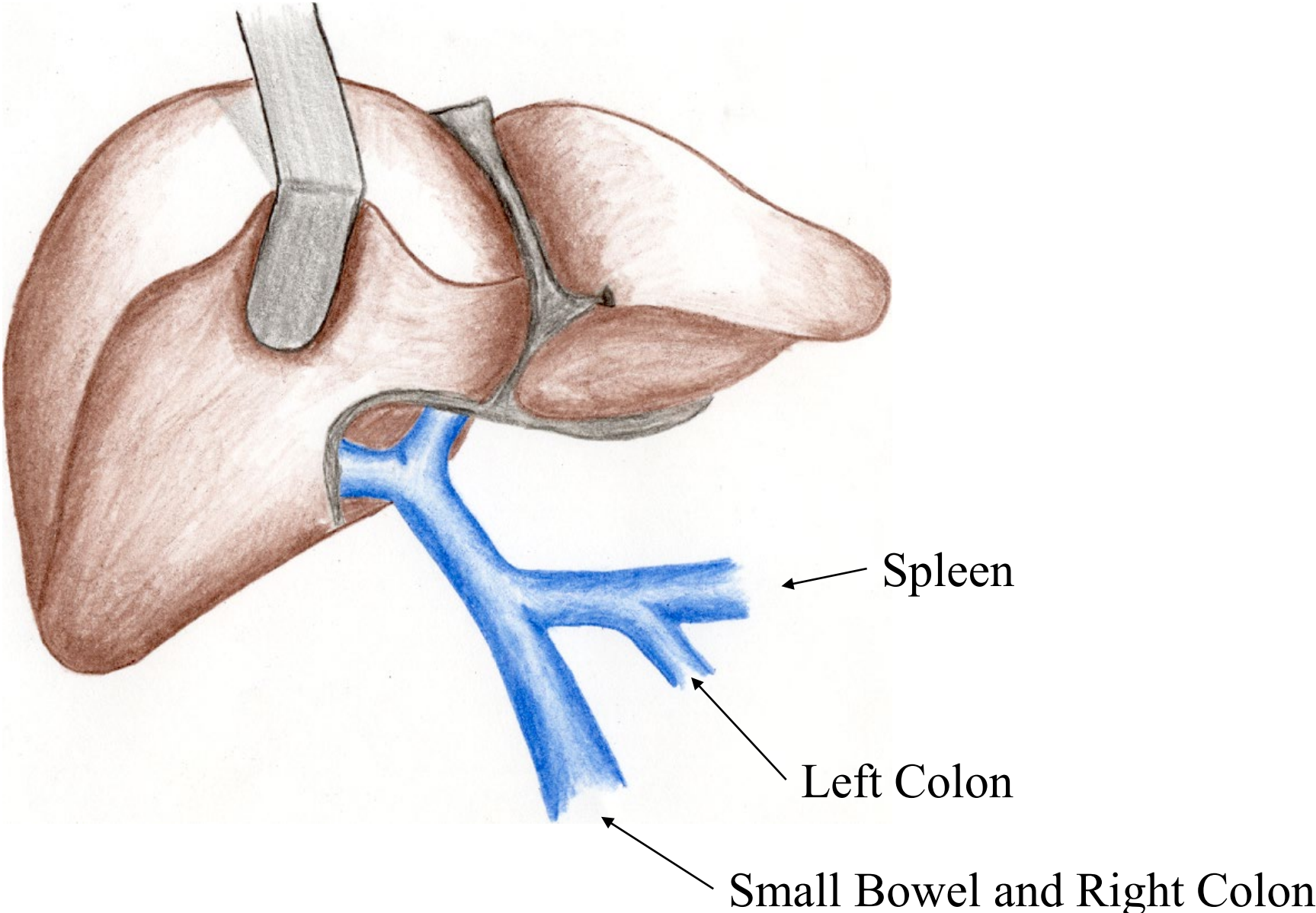
# Liver Anatomy—Portal Vein



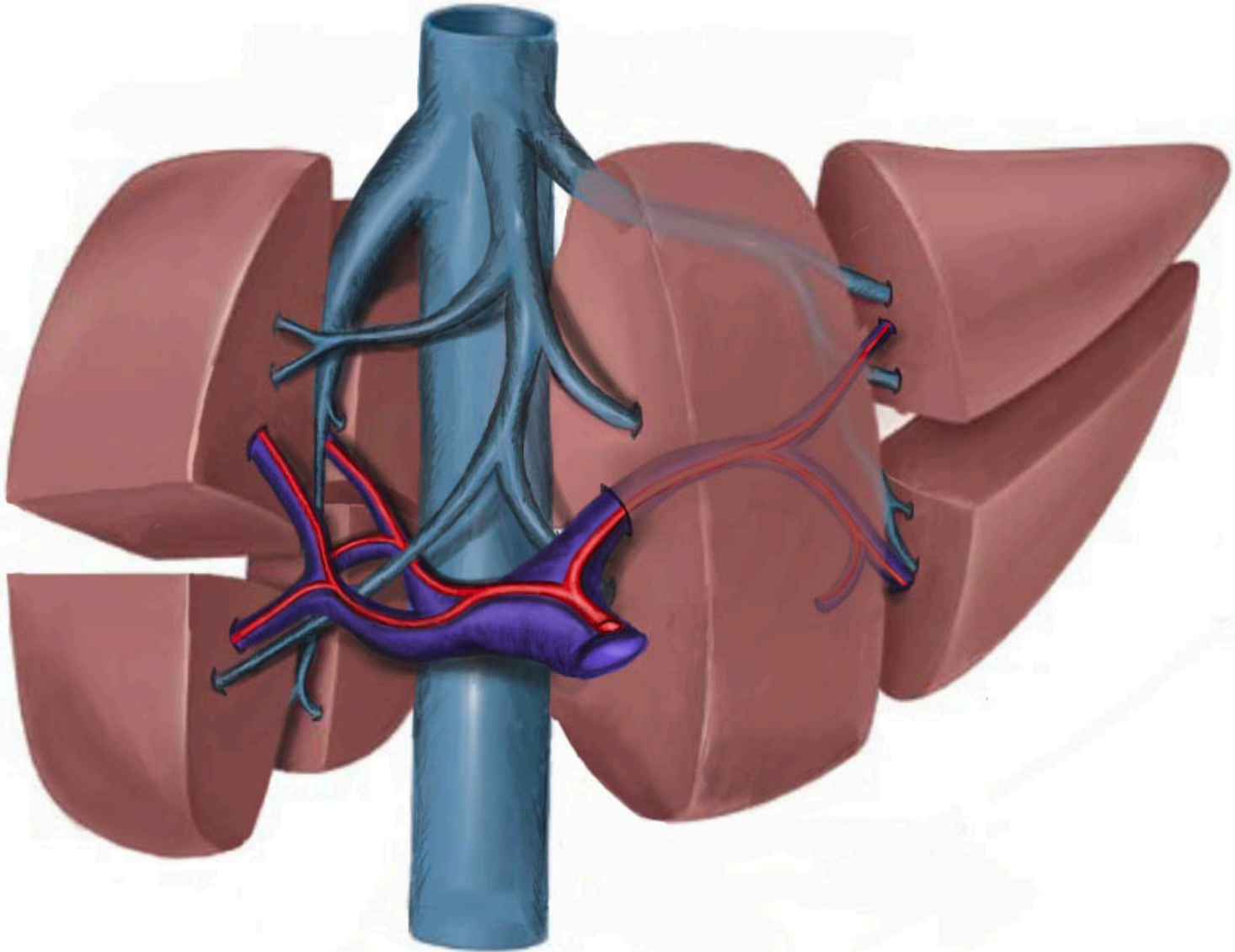
# Liver Anatomy—Couinaud Segments



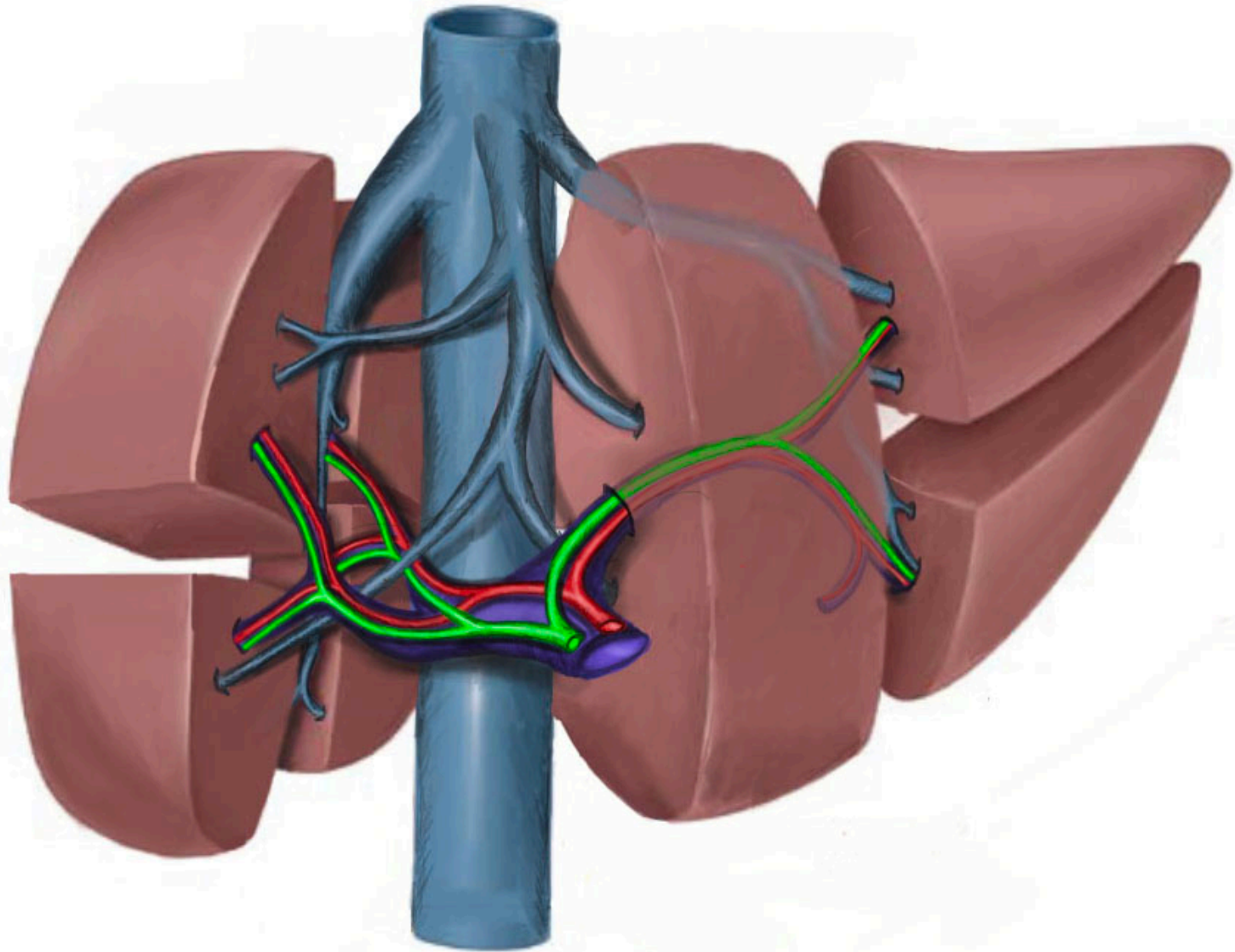
# Liver Anatomy—Portal Vein



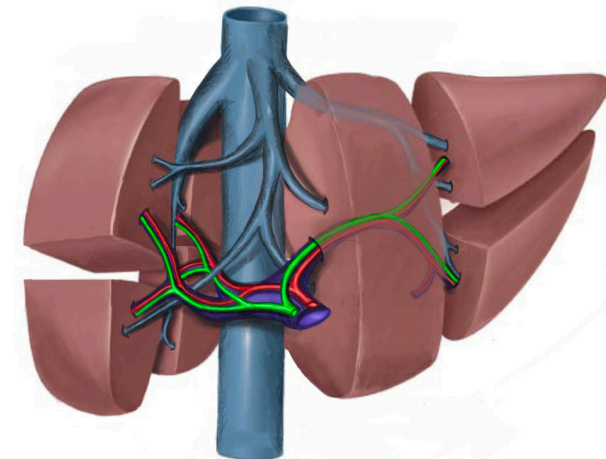
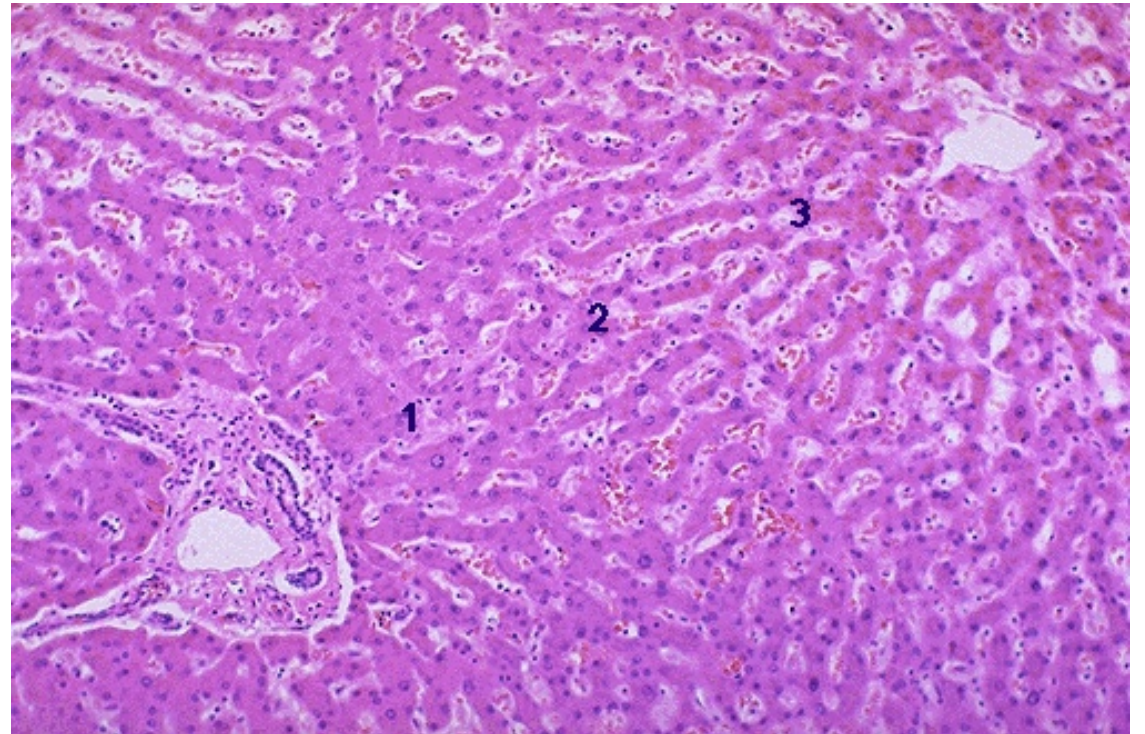
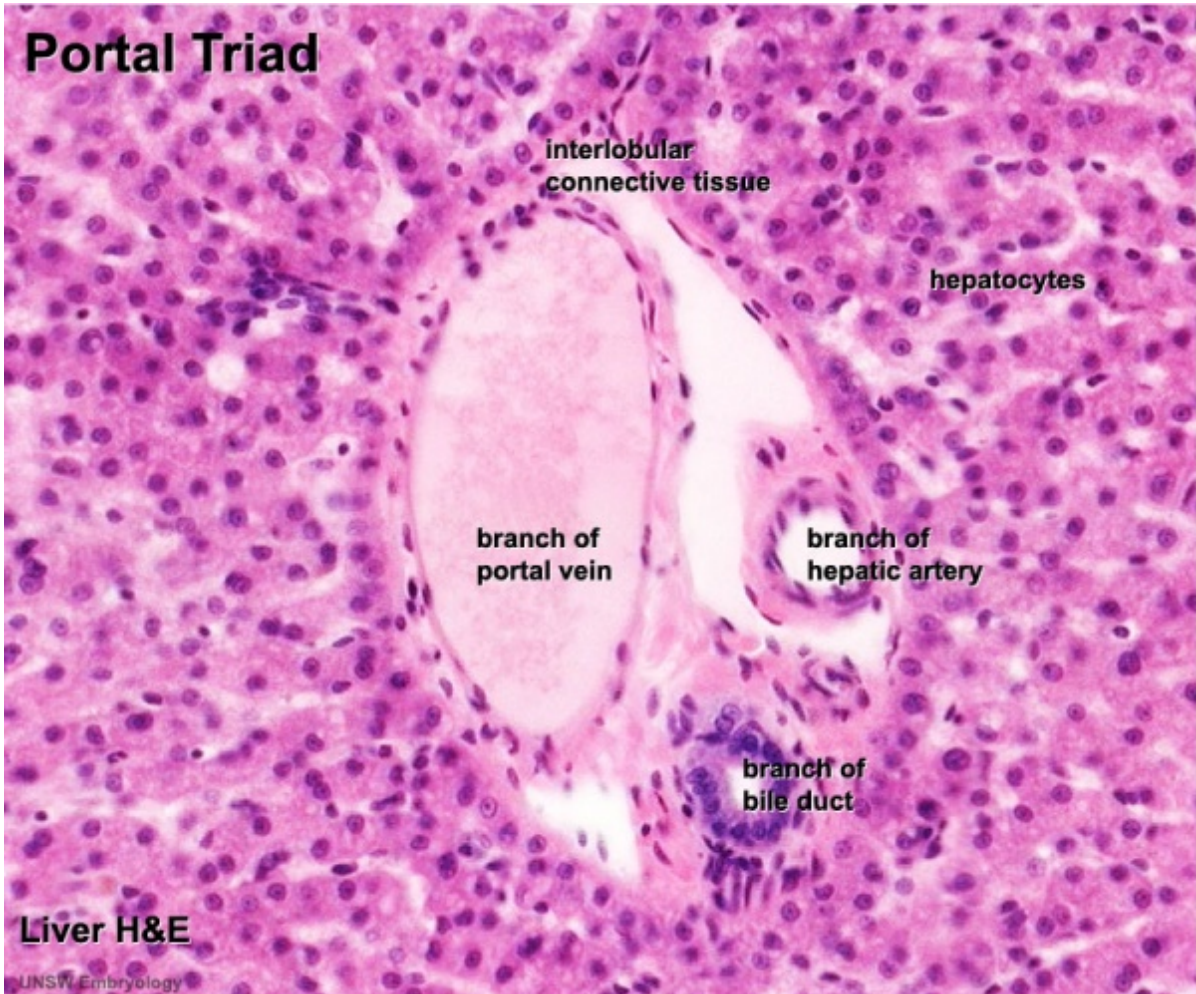
# Liver Anatomy—Hepatic Artery



# Liver Anatomy—Bile Duct

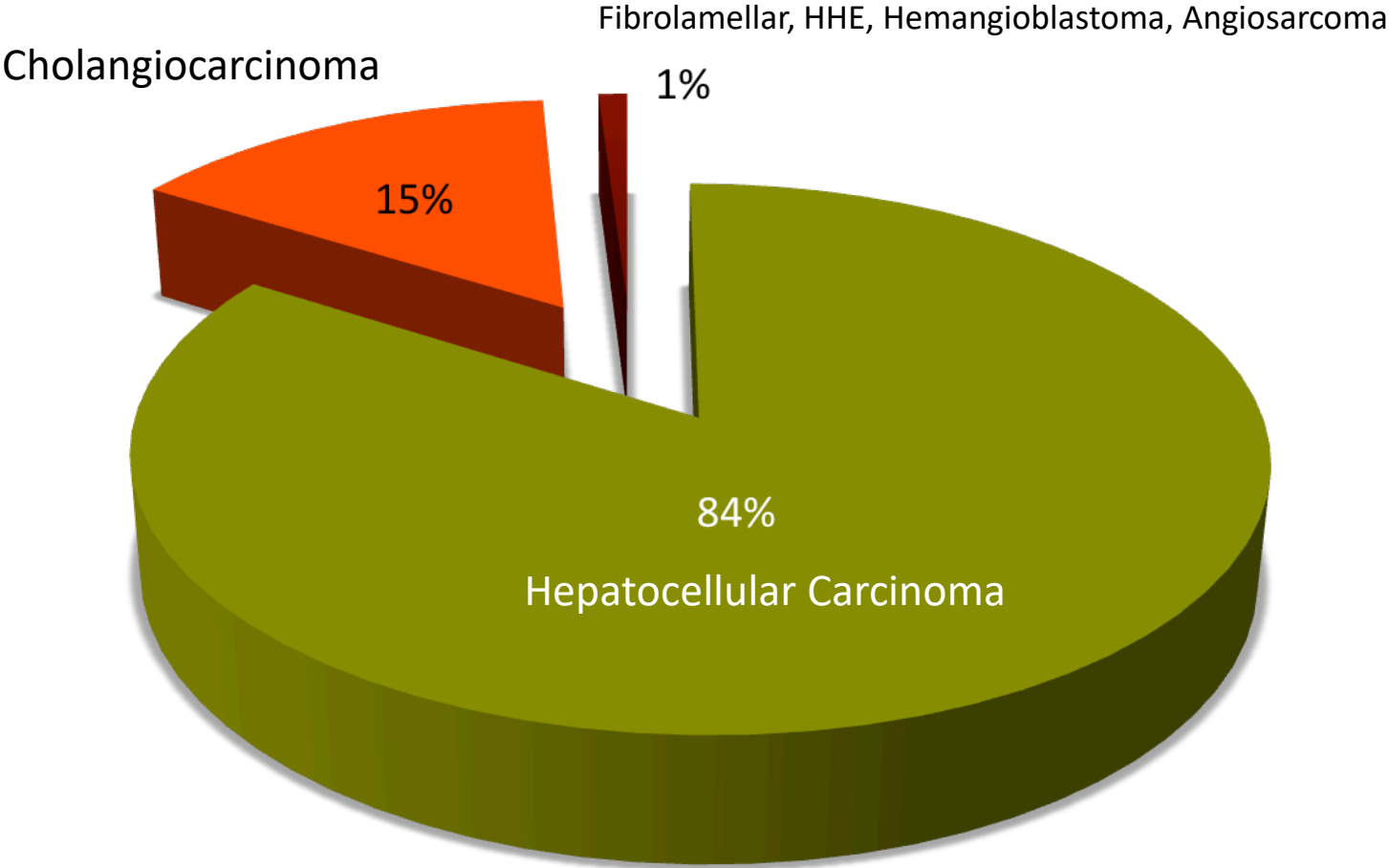


# Liver Anatomy—Portal Triad and Central Vein

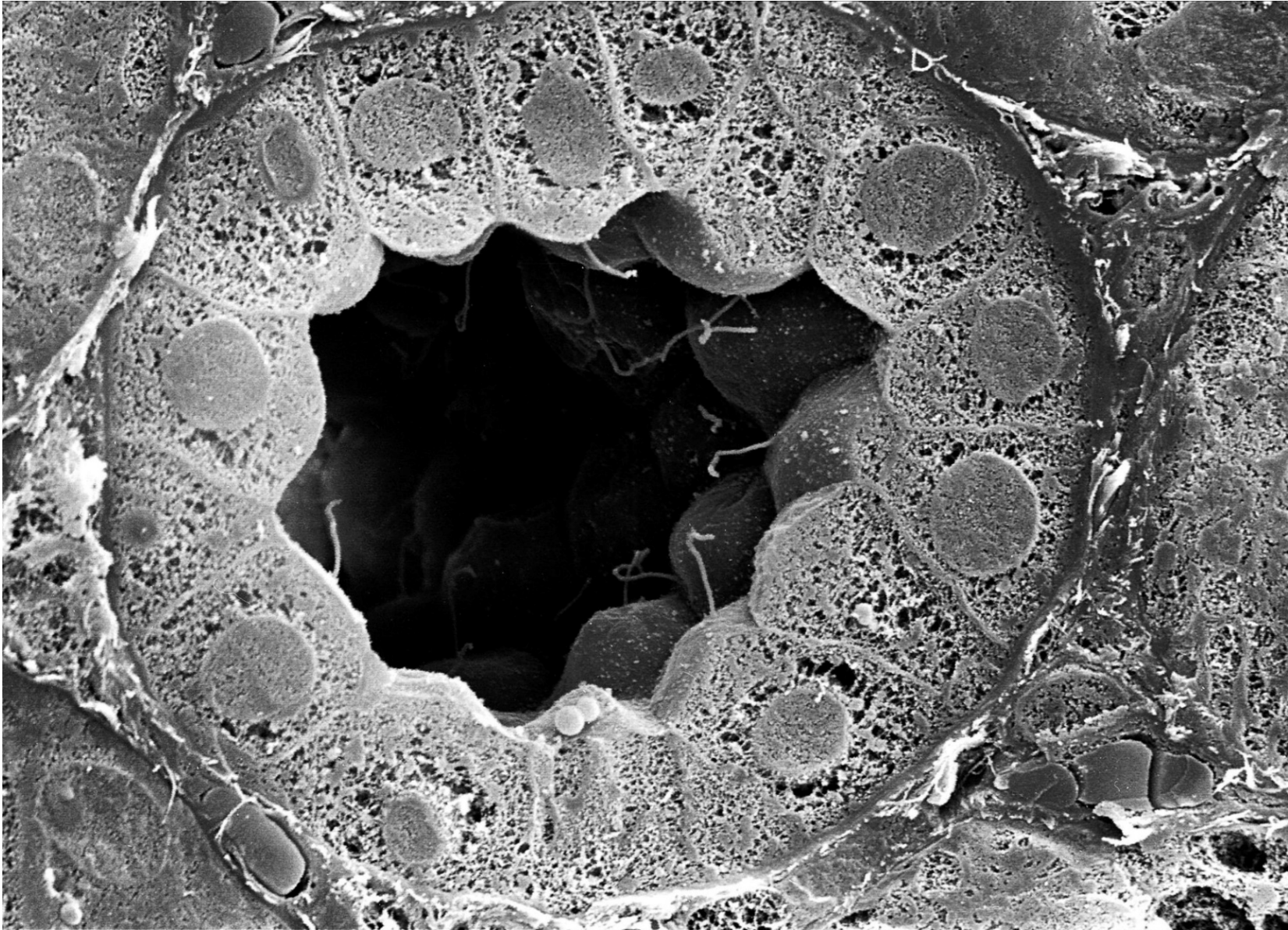




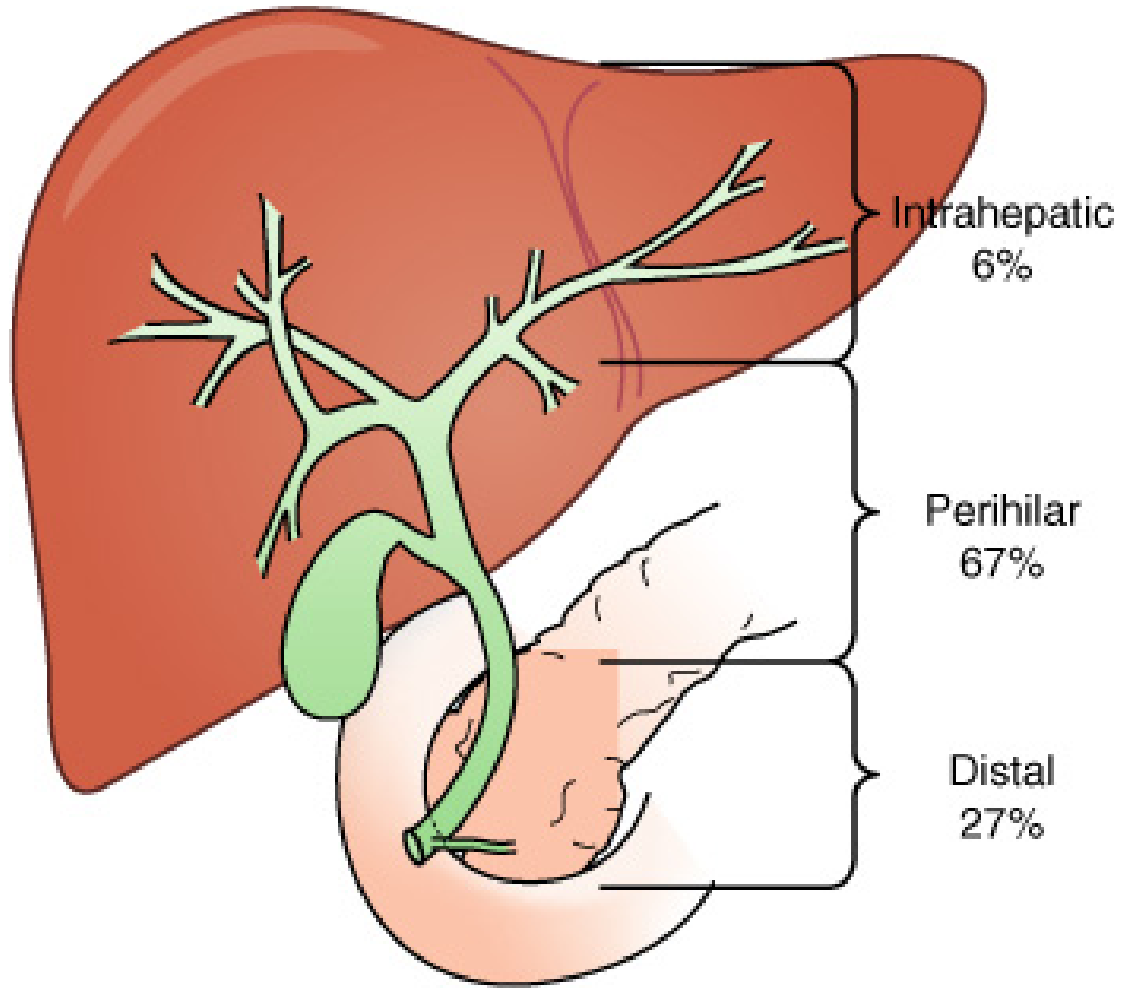
# Types of Liver Cancers



# Cholangiocytes



# Distribution of Cholangiocarcinoma



Copyright © 2004, Elsevier.

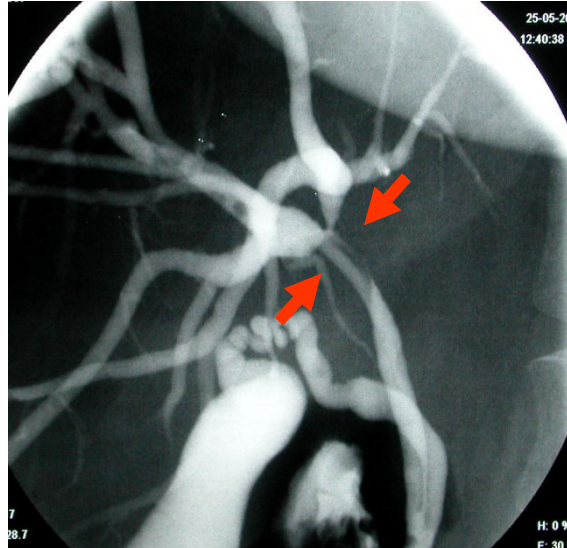
# Distribution of Cholangiocarcinoma

## Intrahepatic/Peripheral



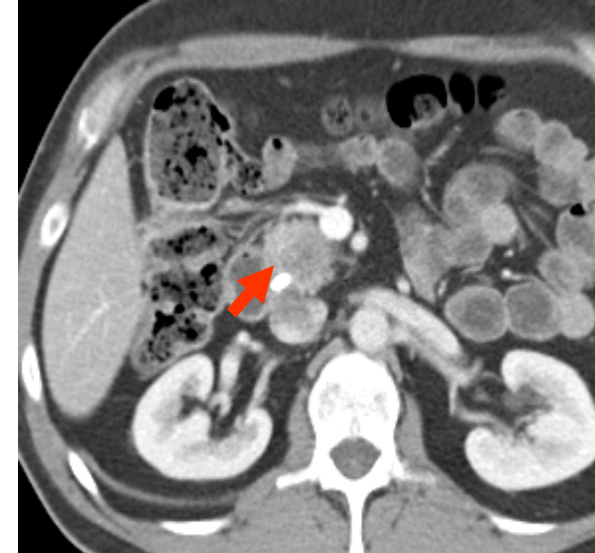
- 7-20%
- Intrahepatic mass
- Cirrhosis uncommon
- Etiology unknown

## Hilar



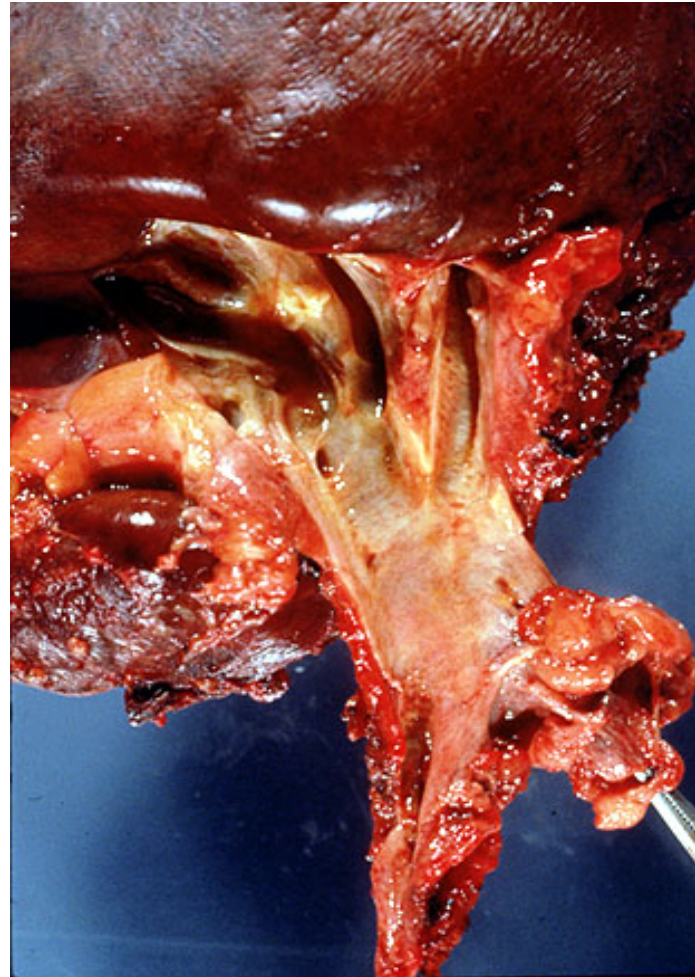
- 40-60%
- Biliary confluence
- Most common

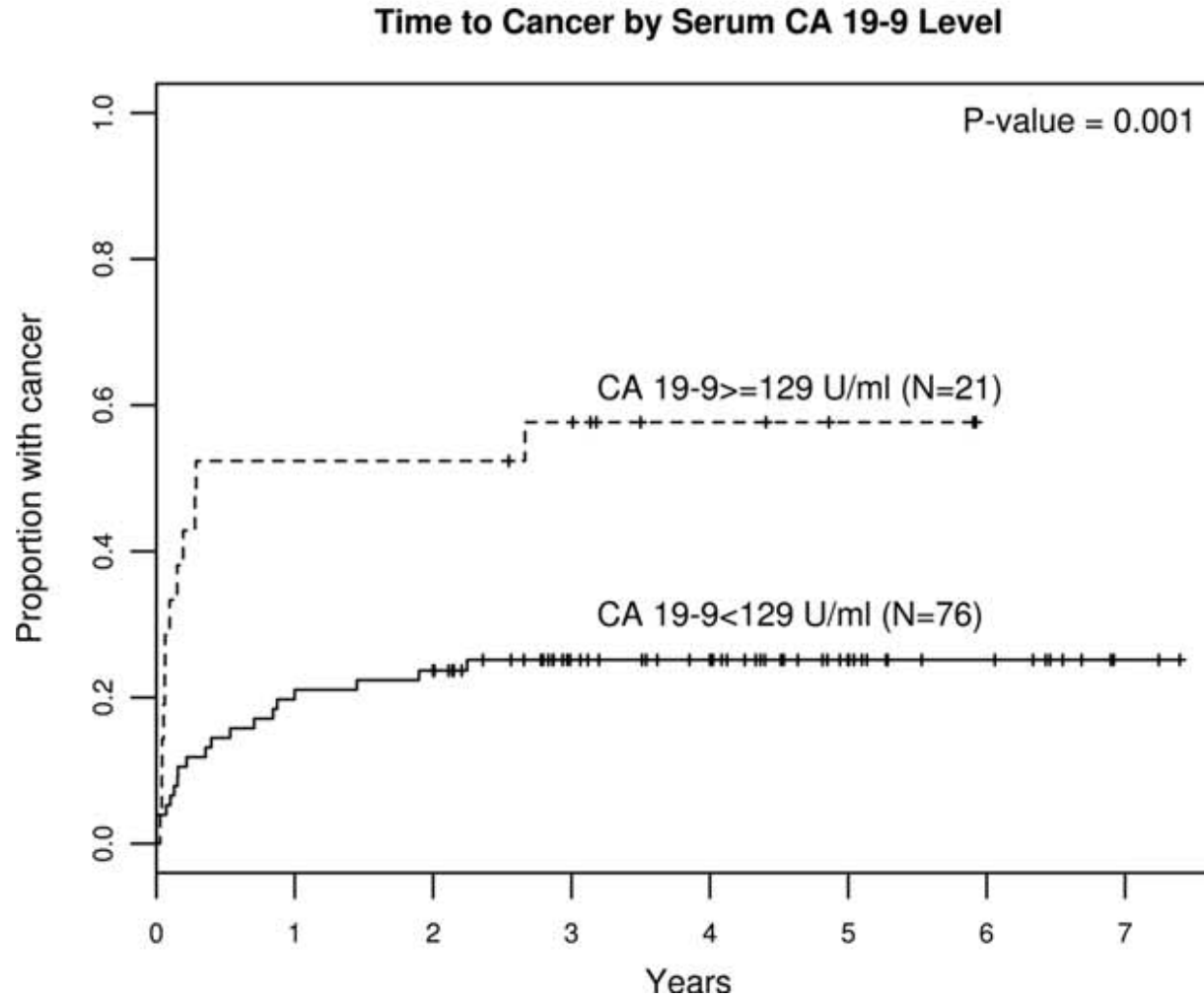
## Distal



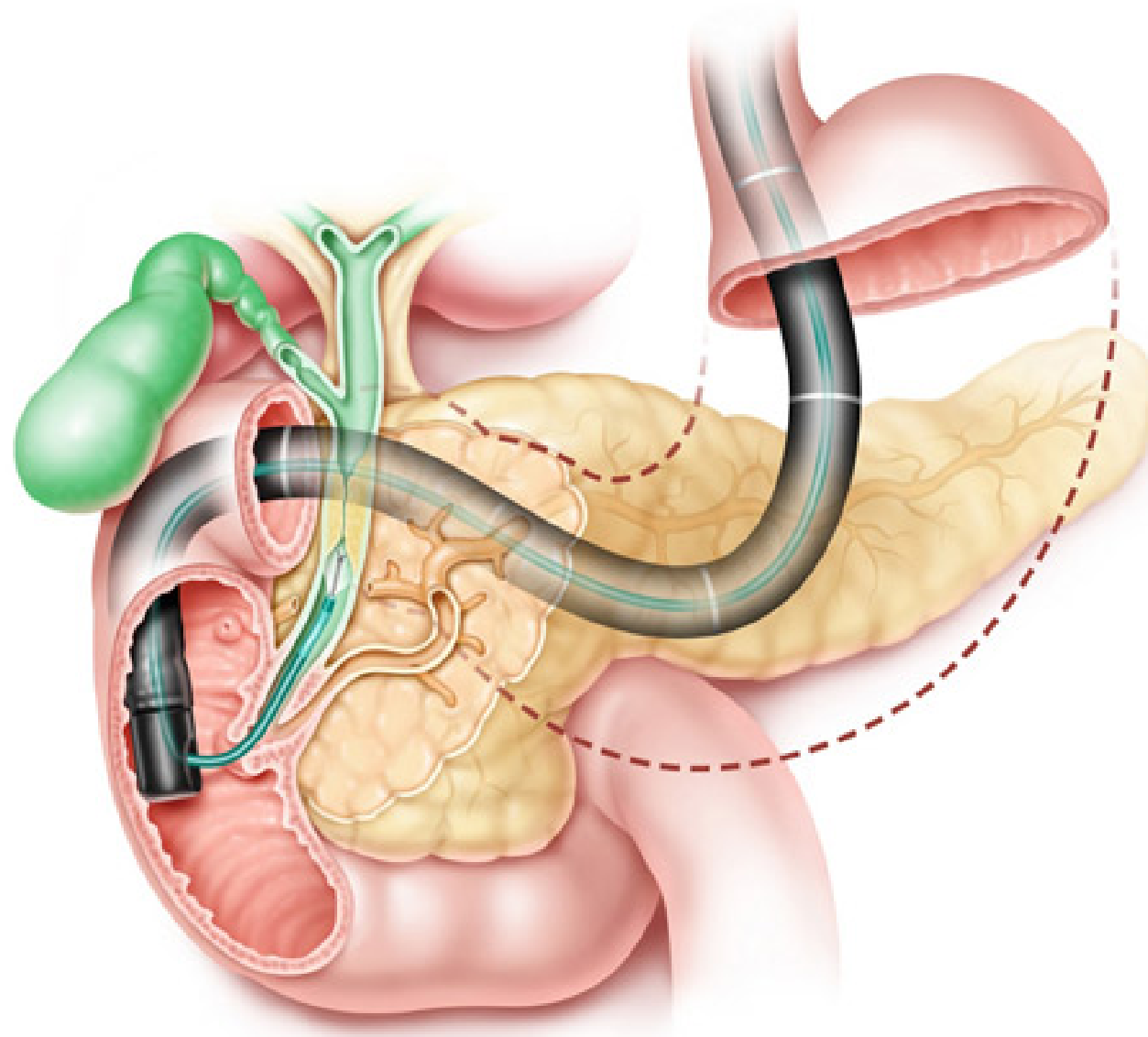
- 20-30%
- 10-15% of peripancreatic tumors

# Cholangiocarcinoma

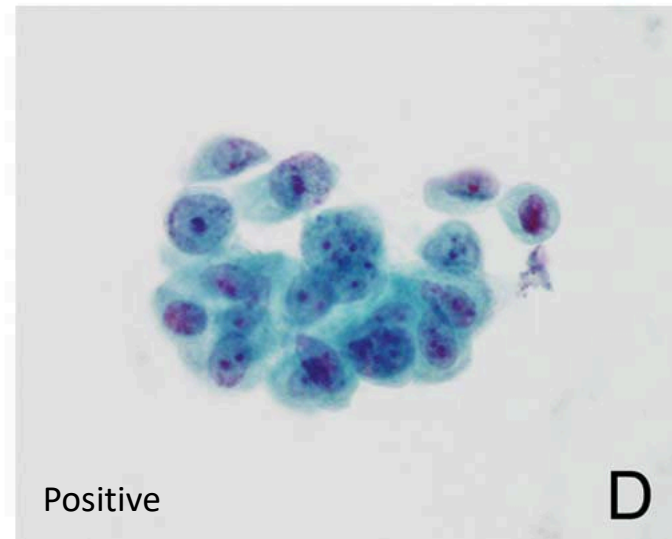
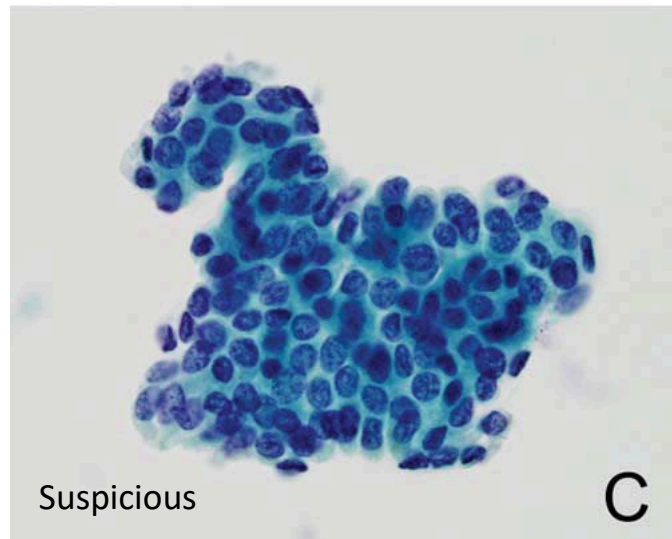
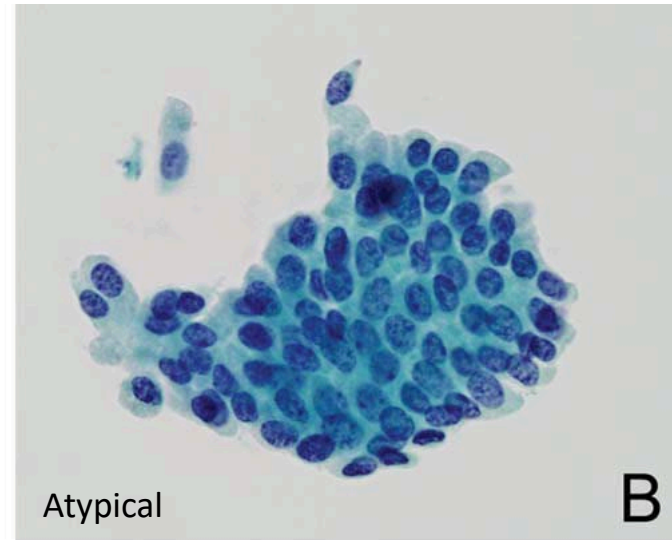
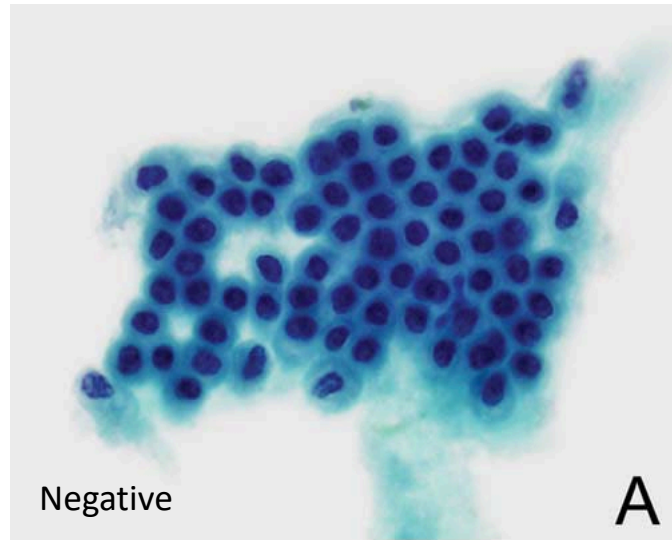




# ERCP with Brushings



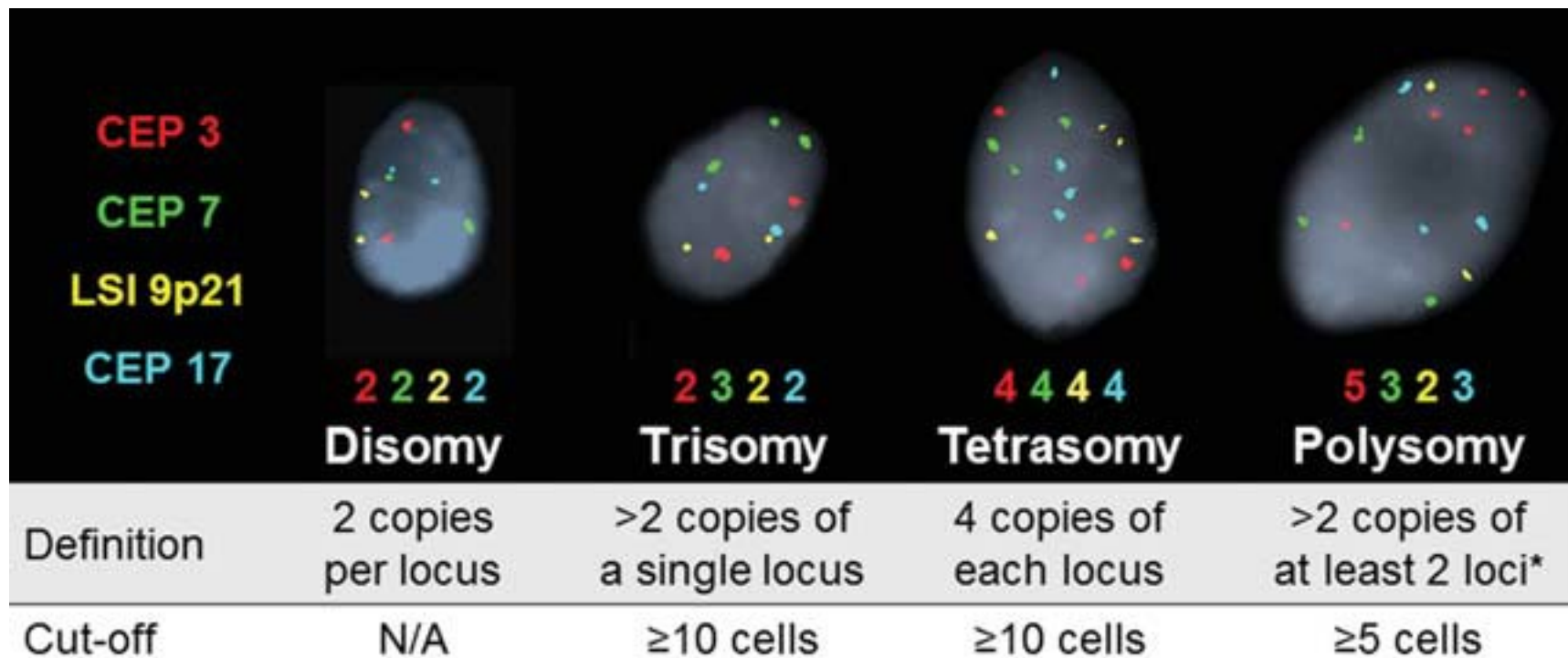
# ERCP with Brushings--Cytology



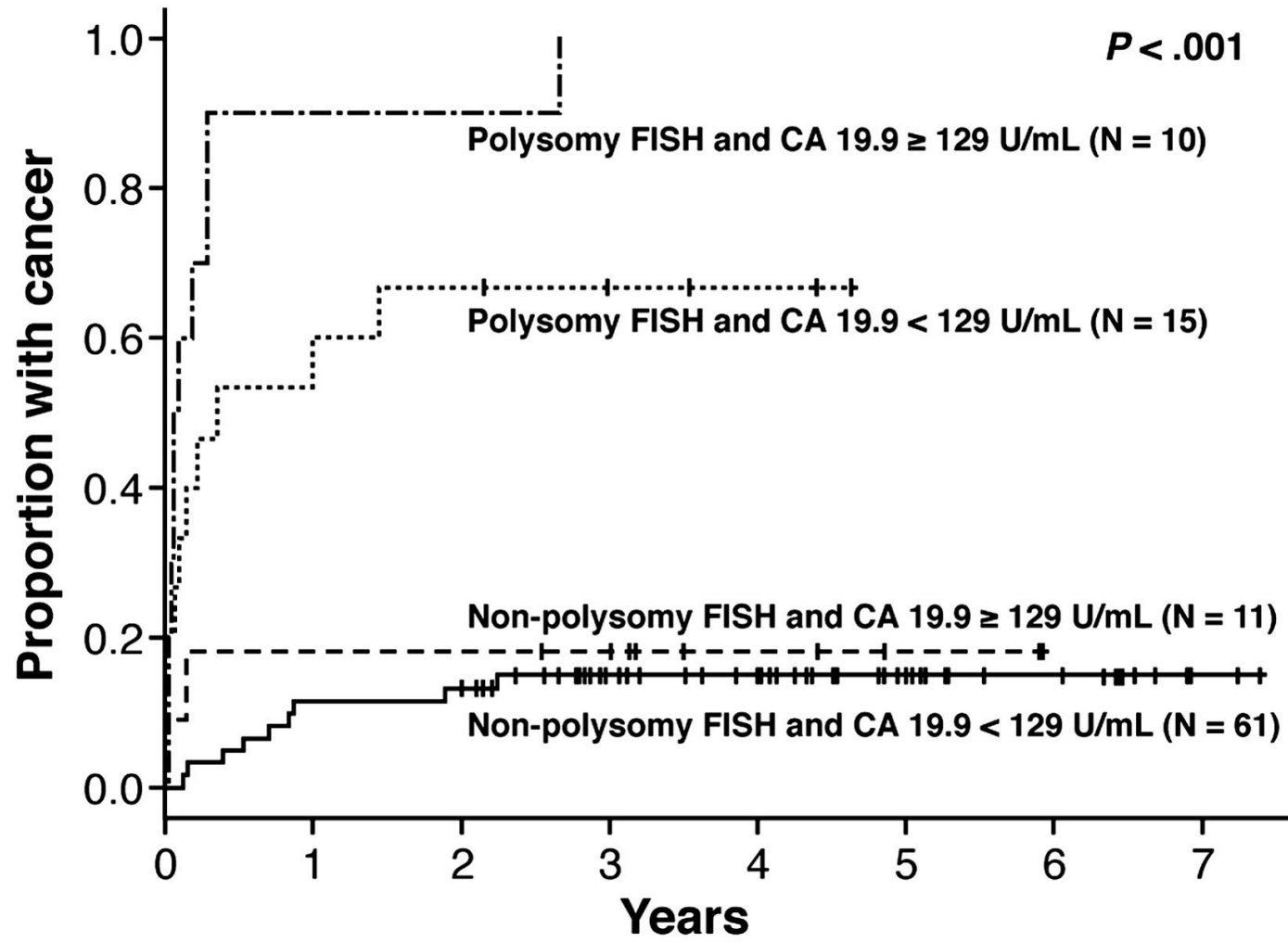


# FISH—Fluorescence in situ hybridization

fluorescence in situ hybridization (FISH)



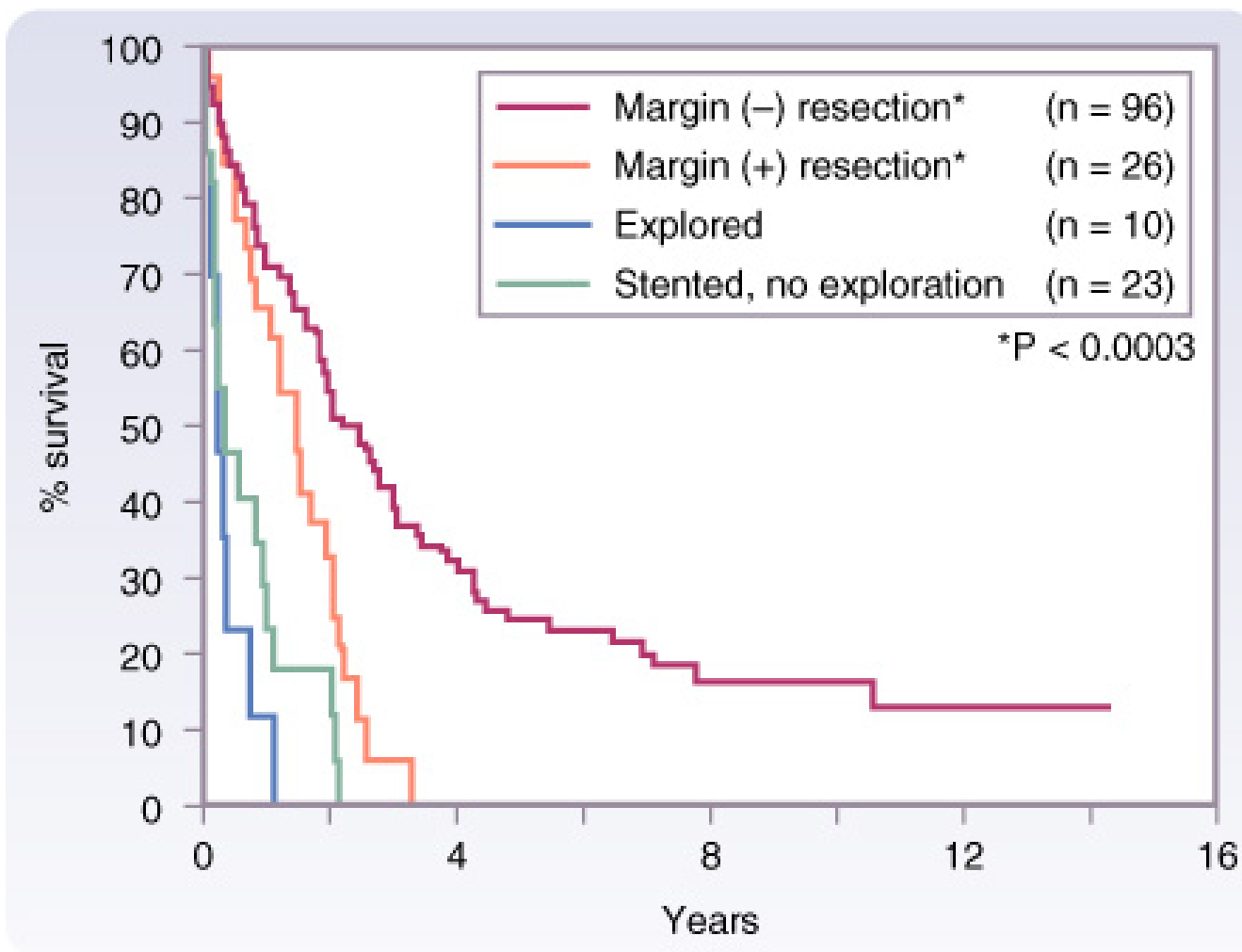
# Combining Tests to Make a Diagnosis



<i>AKT1</i>	<i>ERBB4</i>	<i>GNA11</i>	<i>IDH1</i>	<i>CDKN2A</i>	<i>PTEN</i>	<i>KRAS</i>
<i>ALK</i>	<i>CTNNB1</i>	<i>FGFR1</i>	<i>GNAQ</i>	<i>IDH2</i>	<i>NRAS</i>	<i>PIK3CA</i>
<i>SMAD4</i>	<i>ATM</i>	<i>EGFR</i>	<i>FGFR2</i>	<i>GNAS</i>	<i>KIT</i>	<i>VHL</i>
<i>PDGFRA</i>	<i>TP53</i>	<i>BRAF</i>	<i>ERBB2</i>	<i>FGFR3</i>	<i>HRAS</i>	<i>MET</i>

<i>TP53</i>	52%
<i>KRAS</i>	48%
<i>SMAD4</i>	17%
<i>PIK3CA</i>	10%
<i>GNAS</i>	10%
<i>CTNNB1</i>	10%
<i>CDKN2A</i>	10%
<i>FGFR2</i>	7%
<i>ERBB2</i>	5%
<i>BRAF</i>	5%
<i>ALK</i>	5%
<i>FGFR3</i>	3%

# CCA—Survival without Transplant



Copyright © 2004, Elsevier.

- Cincinnati Transplant Tumor Registry database examined 207 patients who underwent liver transplantation for otherwise unresectable CCA or cholangiohepatoma (mixed HCC/CCA)
- 1, 2, and 5-year survival were 72, 48, and 23%

- **Nebraska** initiated a protocol utilizing radiation for those with unresectable CCA
- 1987-2000: 17 enrolled, 6 were subsequently removed
- median survival from diagnosis of the 11 patients who received liver transplantation is 25 months (range 4–174)

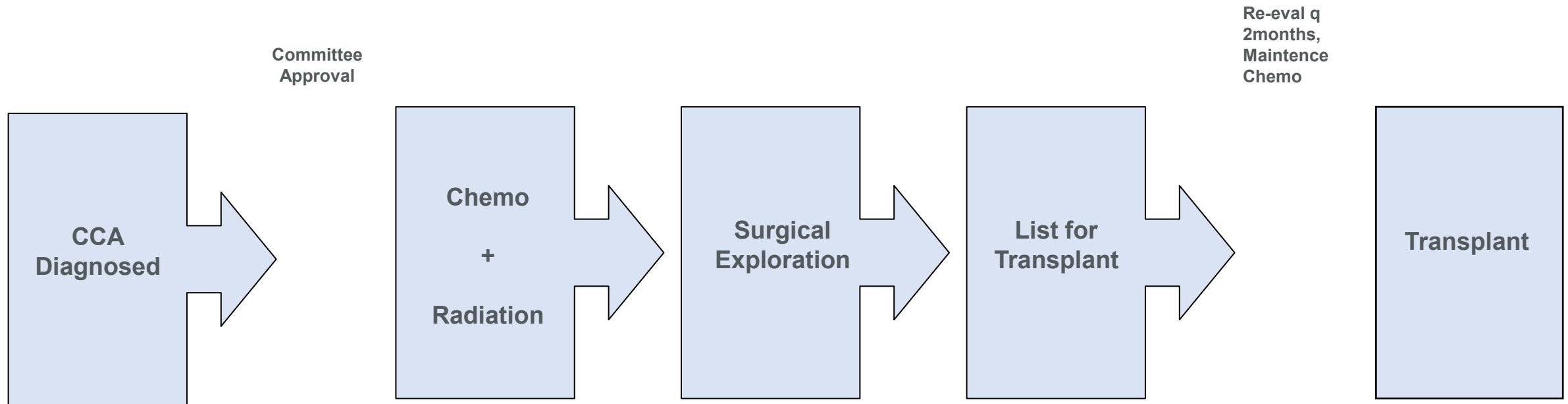




- Restricted inclusion criteria further
- Protracted the radiation over 3 weeks
- Added 5-FU and capecitabine
- Added staging laparotomy after radiotherapy
- 1994-2004: 56 enrolled, 28 were transplanted
  - 6 died post-LTx
  - 88% 1 year and 82% 5 year survival after LTx

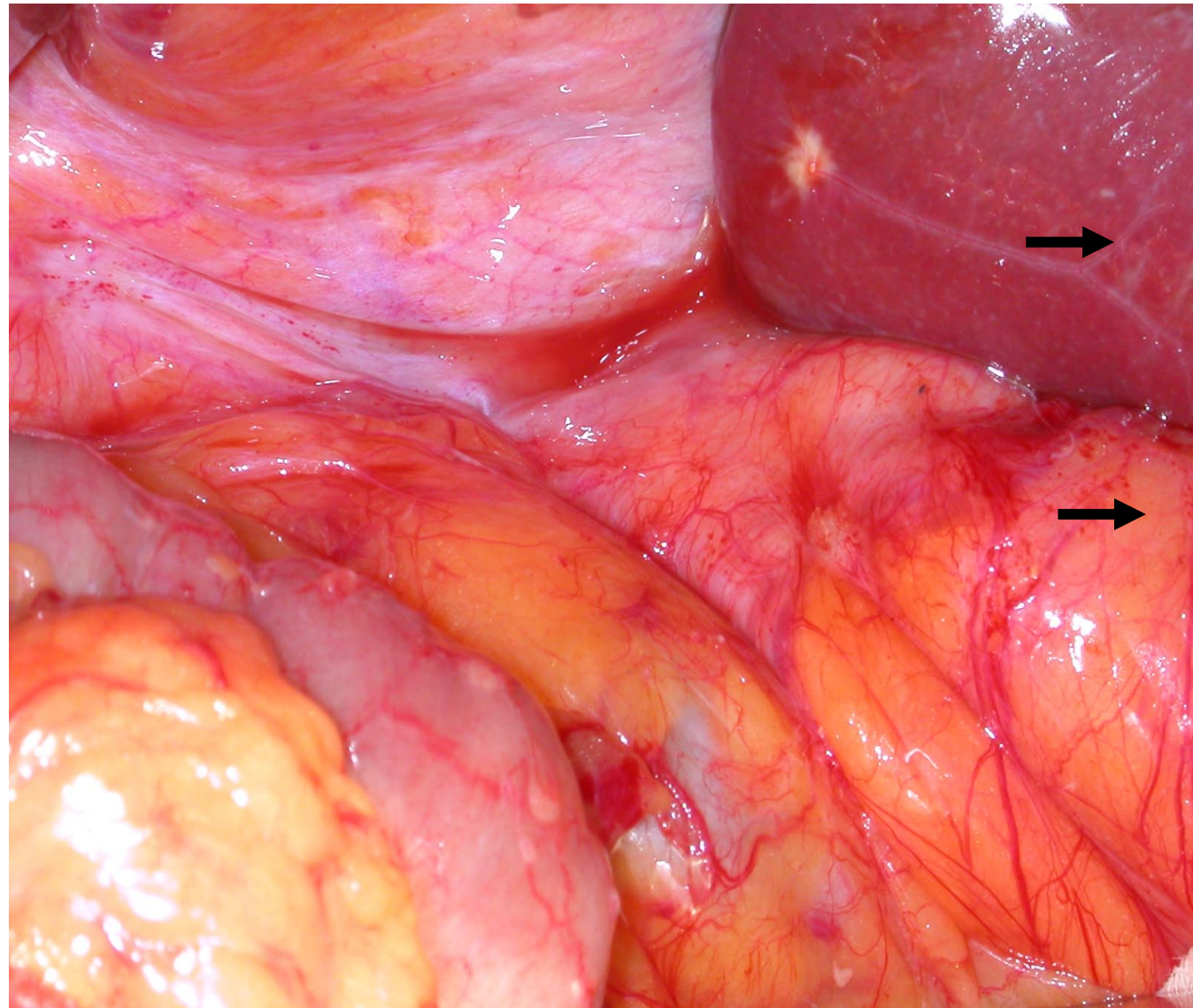


# CCA—"UNOS" Protocol

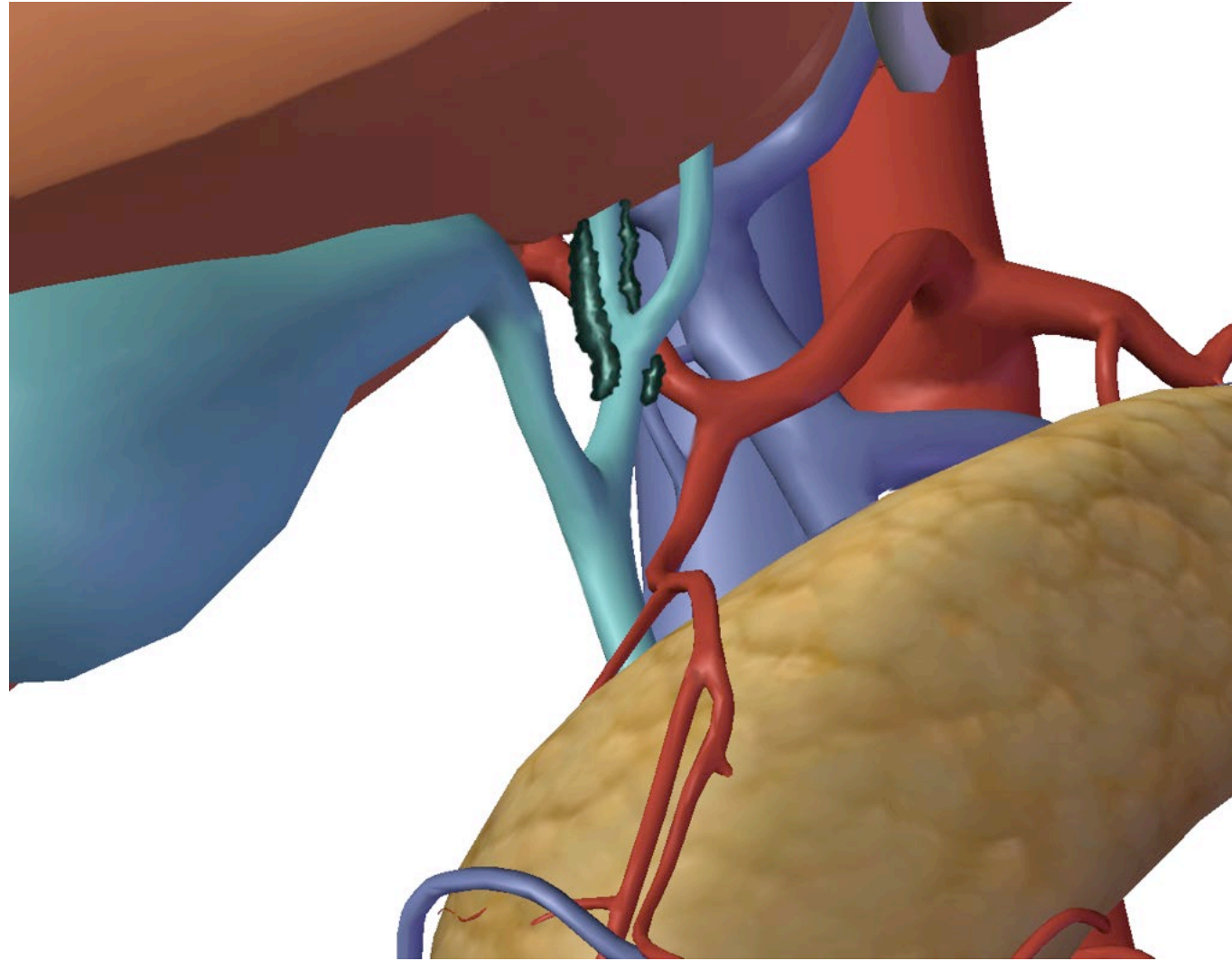


UNOS assigns a MELD score of MMAT-3 for CCA meeting criteria

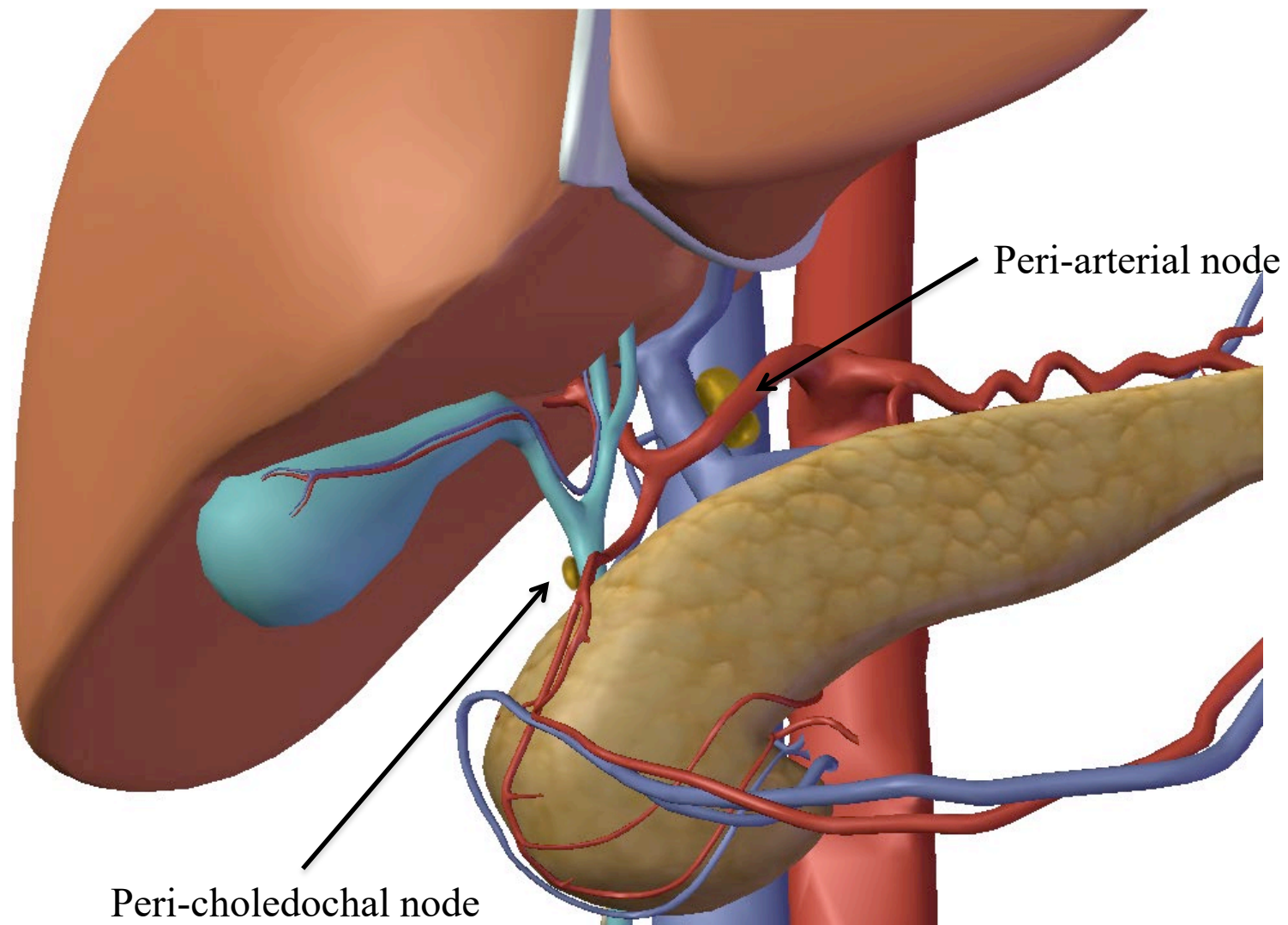
# Surgical Exploration—Look for Peritoneal Mets



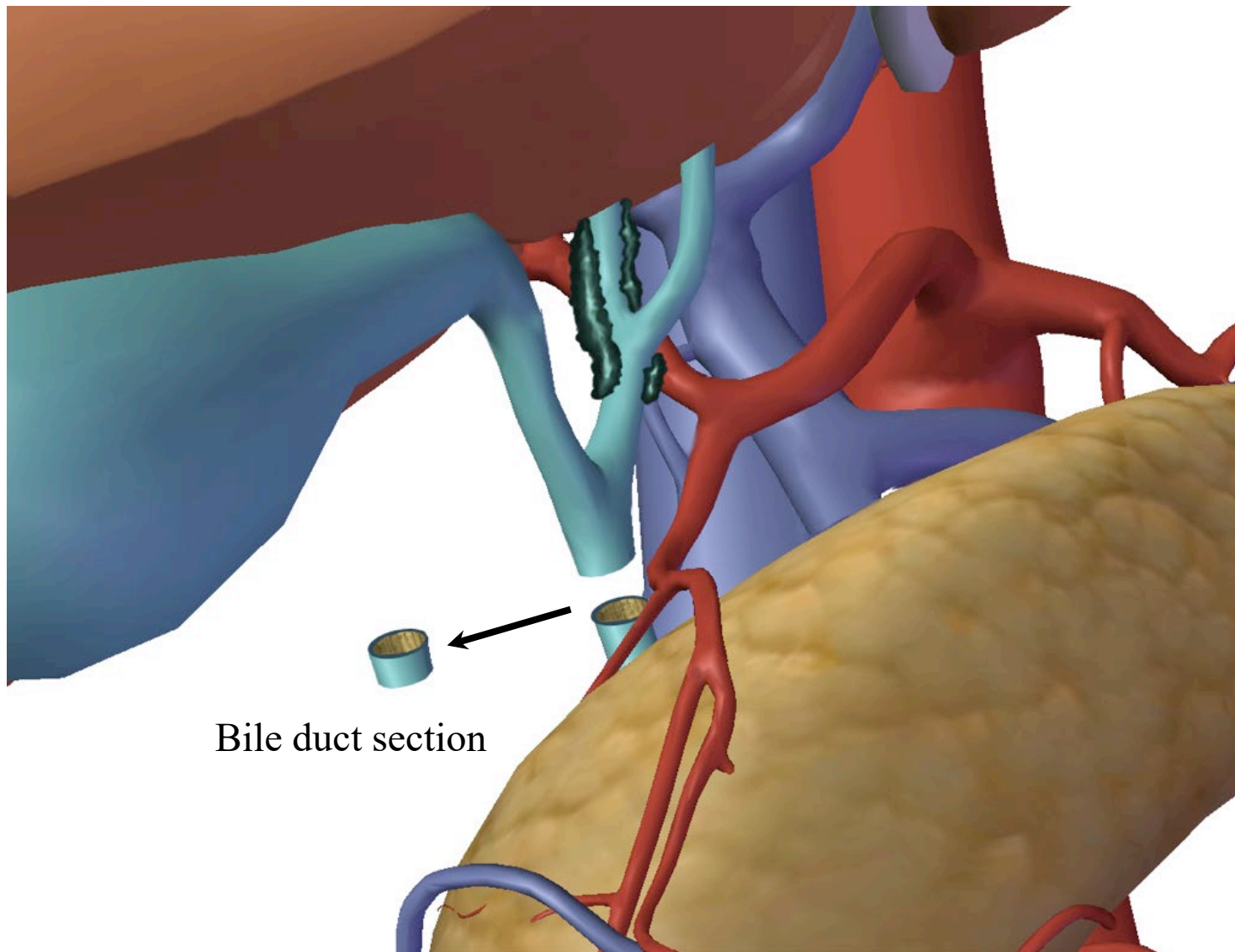
## Surgical Exploration—Stay Away from Tumor



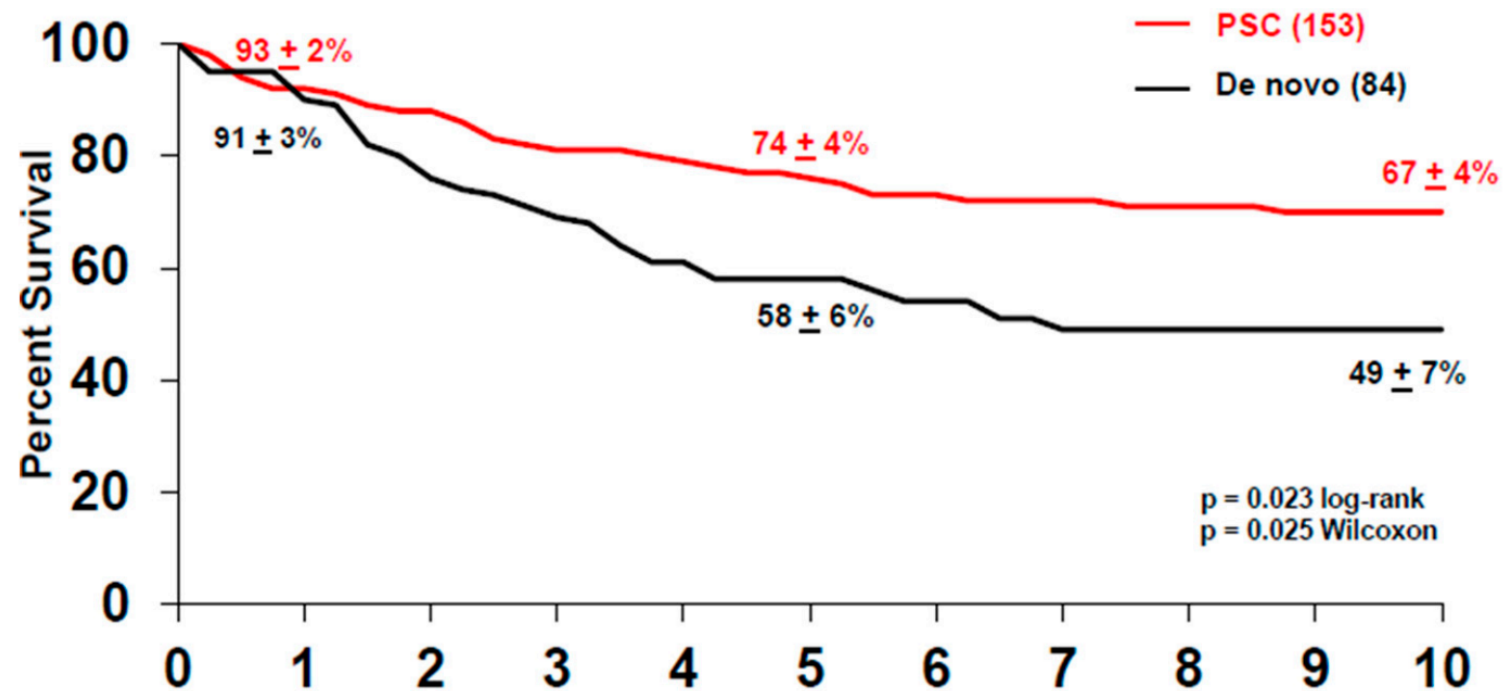
## Surgical Exploration—Look for Nodal Mets



# Surgical Exploration—Assess Distal Bile Duct Spread



# Survival for Hilar CCA—Mayo (UNOS) Protocol



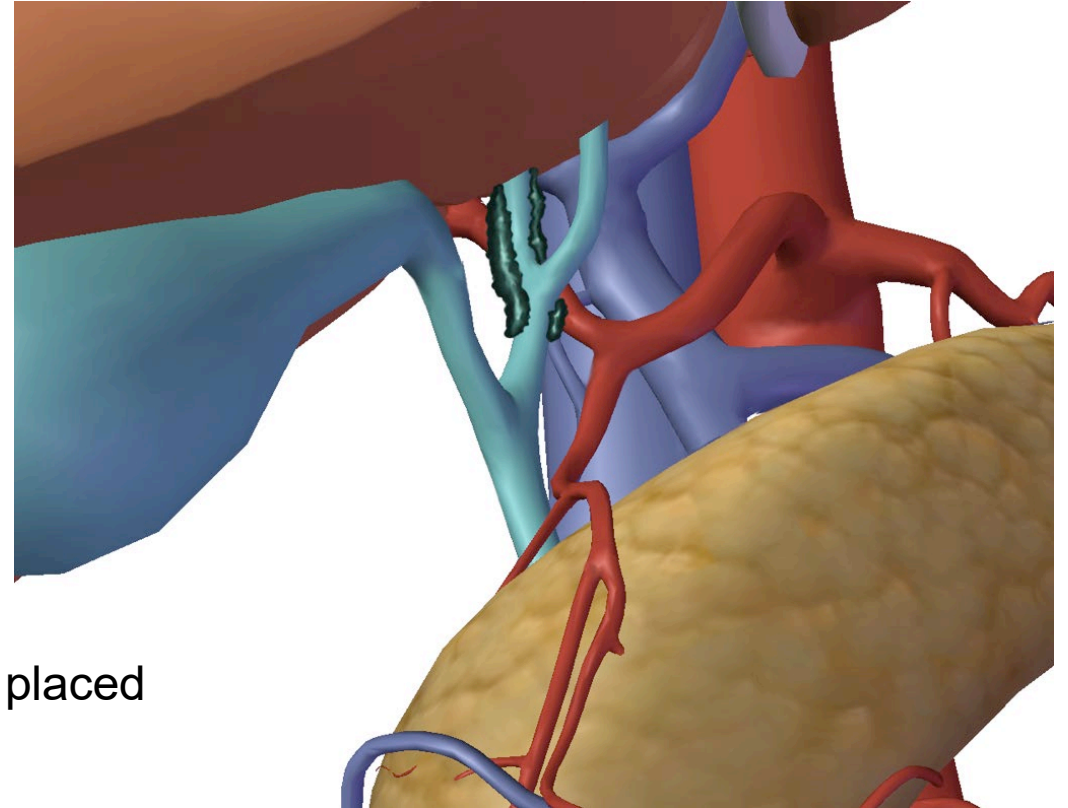
**Figure 2.** Survival after liver transplantation of patients with de novo (black) and primary sclerosing cholangitis (PSC)-associated pCCA (red). Patients who were transplanted for PSC-associated pCCA had better long-term survival when compared to patients transplanted for de novo pCCA.

40 year-old male

Diagnosed with PSC in 2012

Jan 2017—presented with jaundice

ERCP showed strictures and stents were placed



ERCP 3/29/17:

Cytology negative:

DUCTAL CELLS AND SEVERE ACUTE INFLAMMATION  
MALIGNANT CELLS NOT IDENTIFIED

FISH Positive:

Abnormal Cell Line - A total of fifty interphase nuclei were analyzed, and 44 cells showed **polysomy** for chromosomes 3, 7, and/or 17 (containing three or more copies of at least two of those chromosomes). Polysomy of chromosome 9 was not observed.

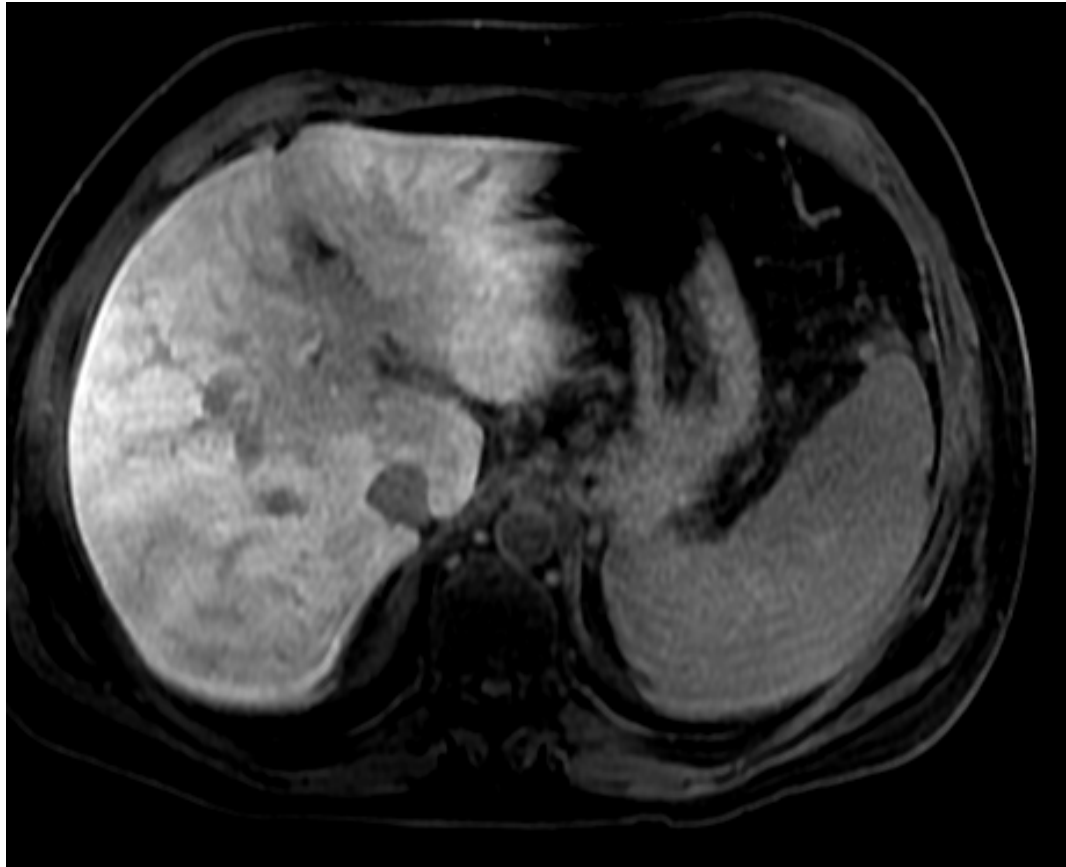
DIAGNOSIS: POLYSOMY - The results of this test are considered positive. Polysomy of multiple chromosomes has been associated with pancreatobiliary tract malignancies.

Ca19-9

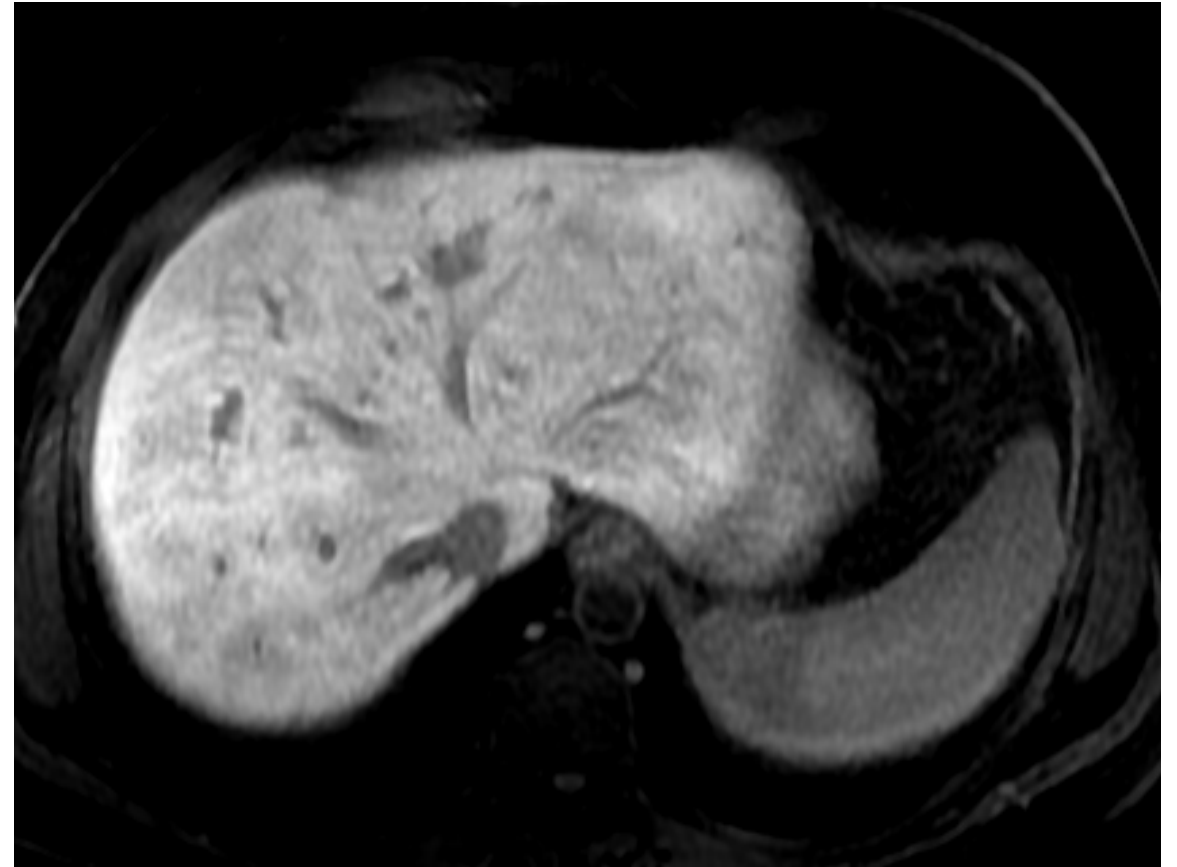
20 ng/mL



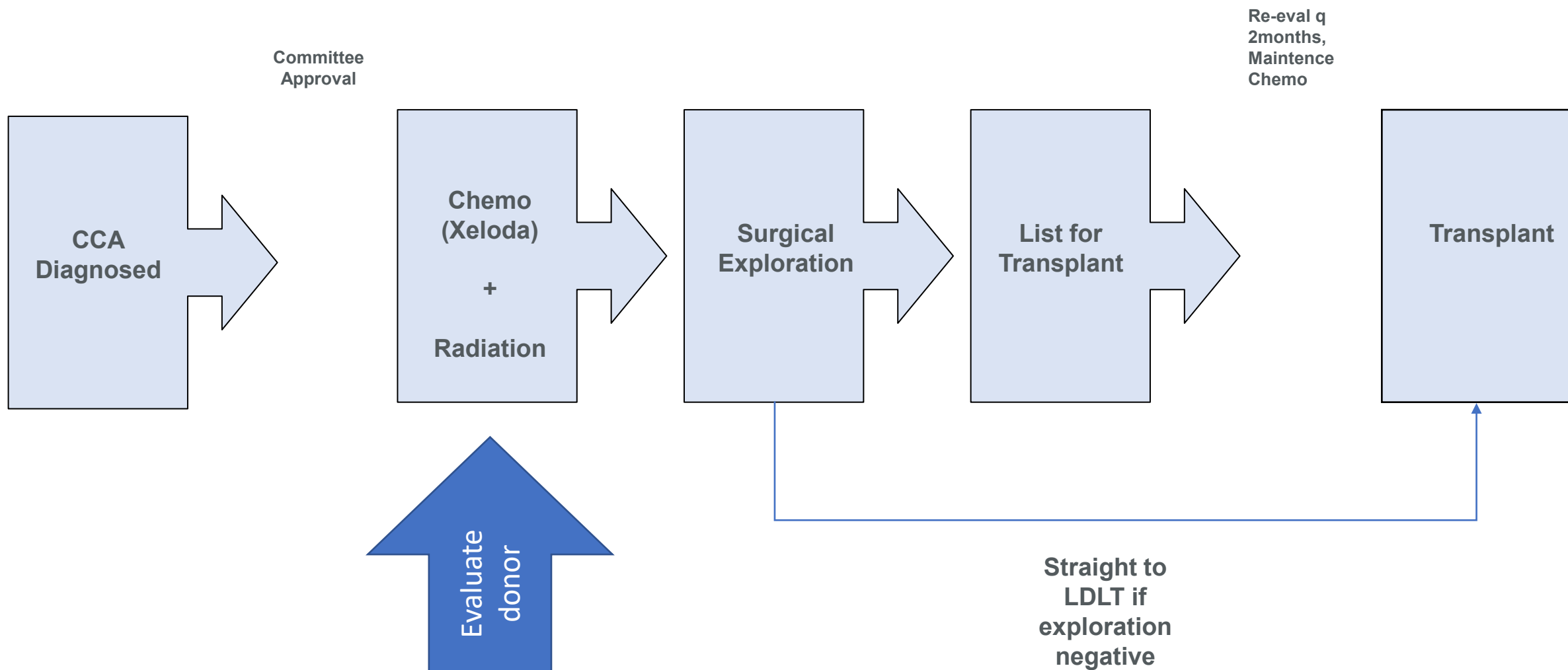
Pre-transplant  
MRI with Eovist  
Central decreased uptake of Eovist



Ductal dilatation



# UPMC LDLT Track for CCA



Path at Exploration:

PART 1: HEPATIC ARTERY LYMPH NODE, EXCISION:

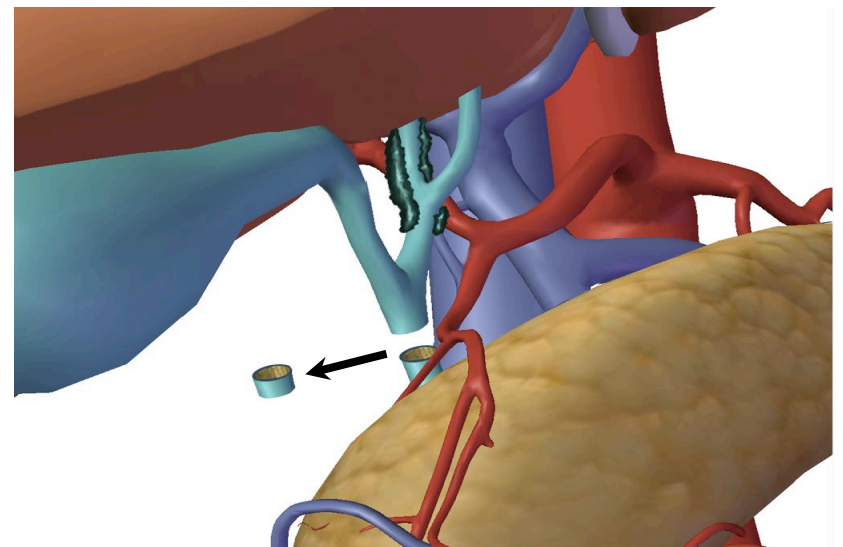
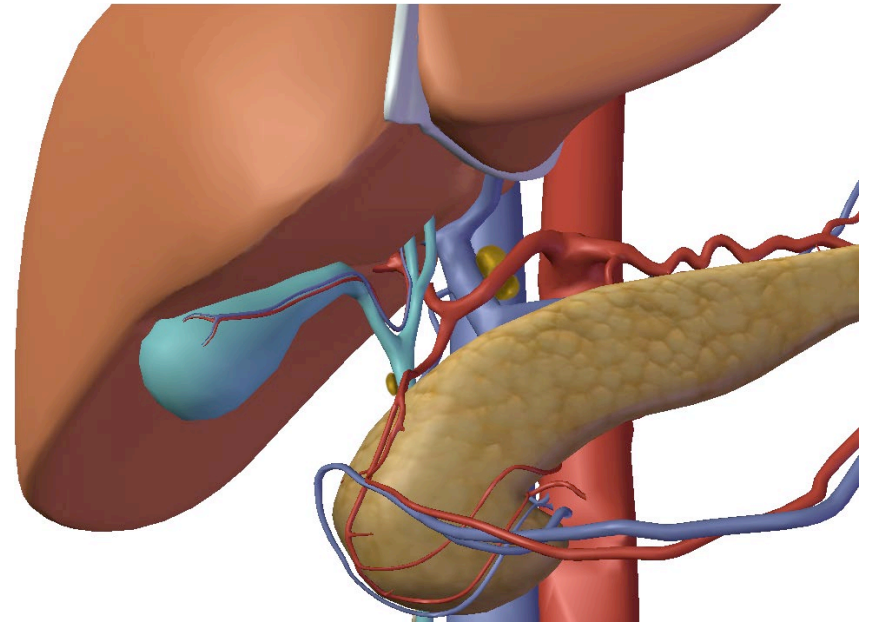
- A. REACTIVE LYMPH NODE.
- B. NO TUMOR SEEN.

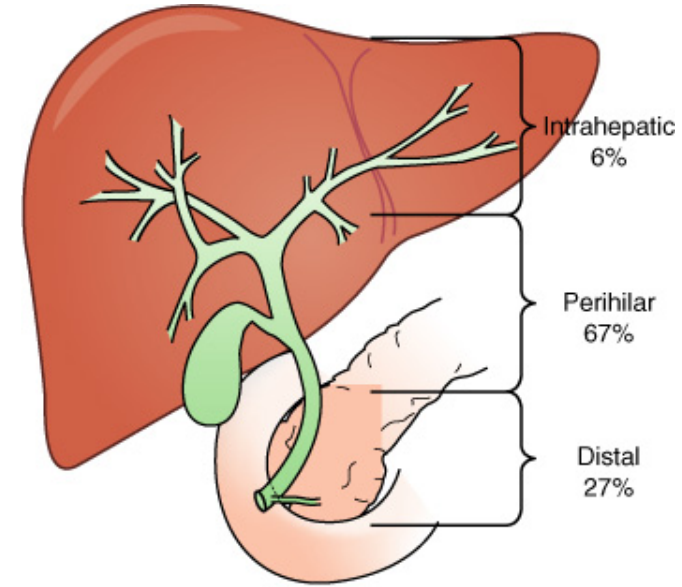
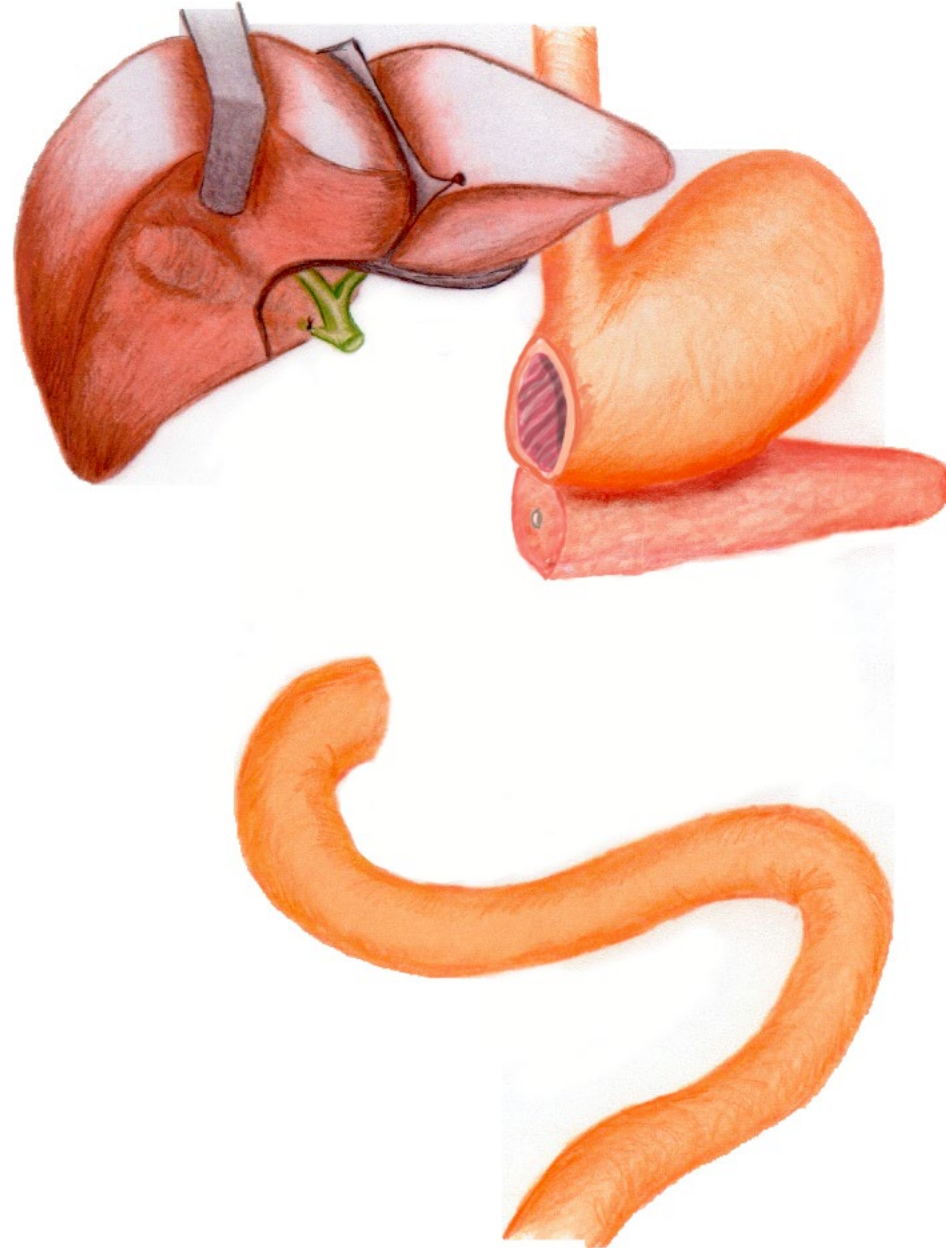
PART 2: BILE DUCT LYMPH NODE, EXCISION:

- A. REACTIVE LYMPH NODE.
- B. NO TUMOR SEEN.

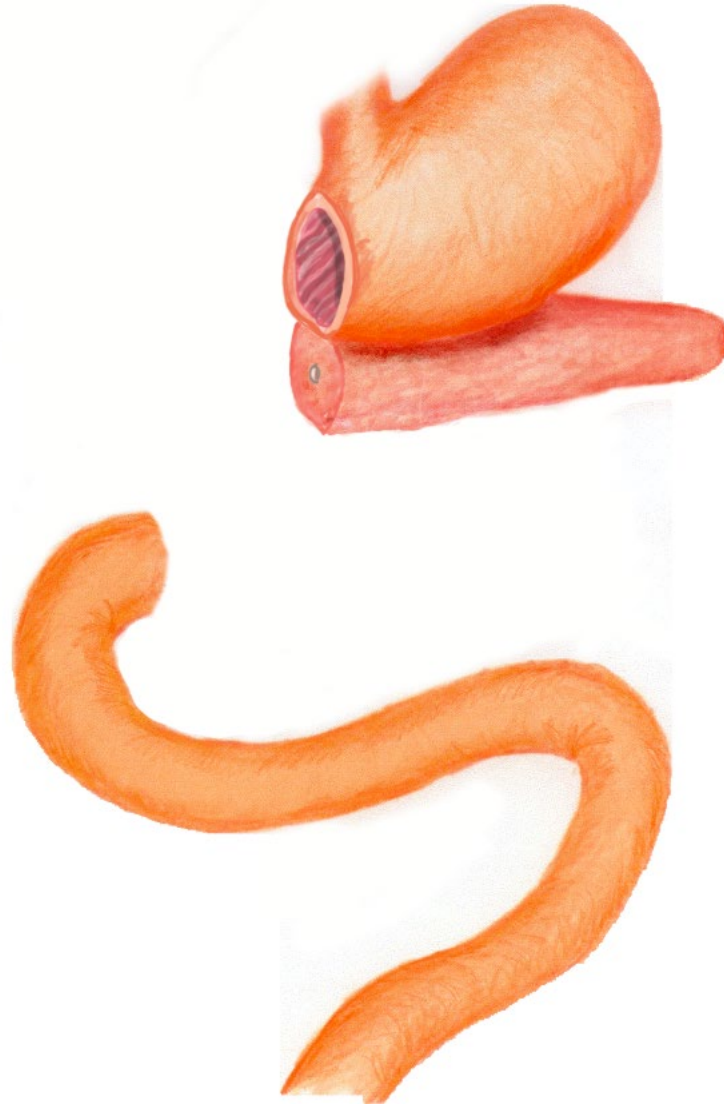
PART 3: COMMON BILE DUCT, DISTAL MARGIN:  
**CHOLANGIOCARCINOMA**, MODERATED DIFFERENTIATED

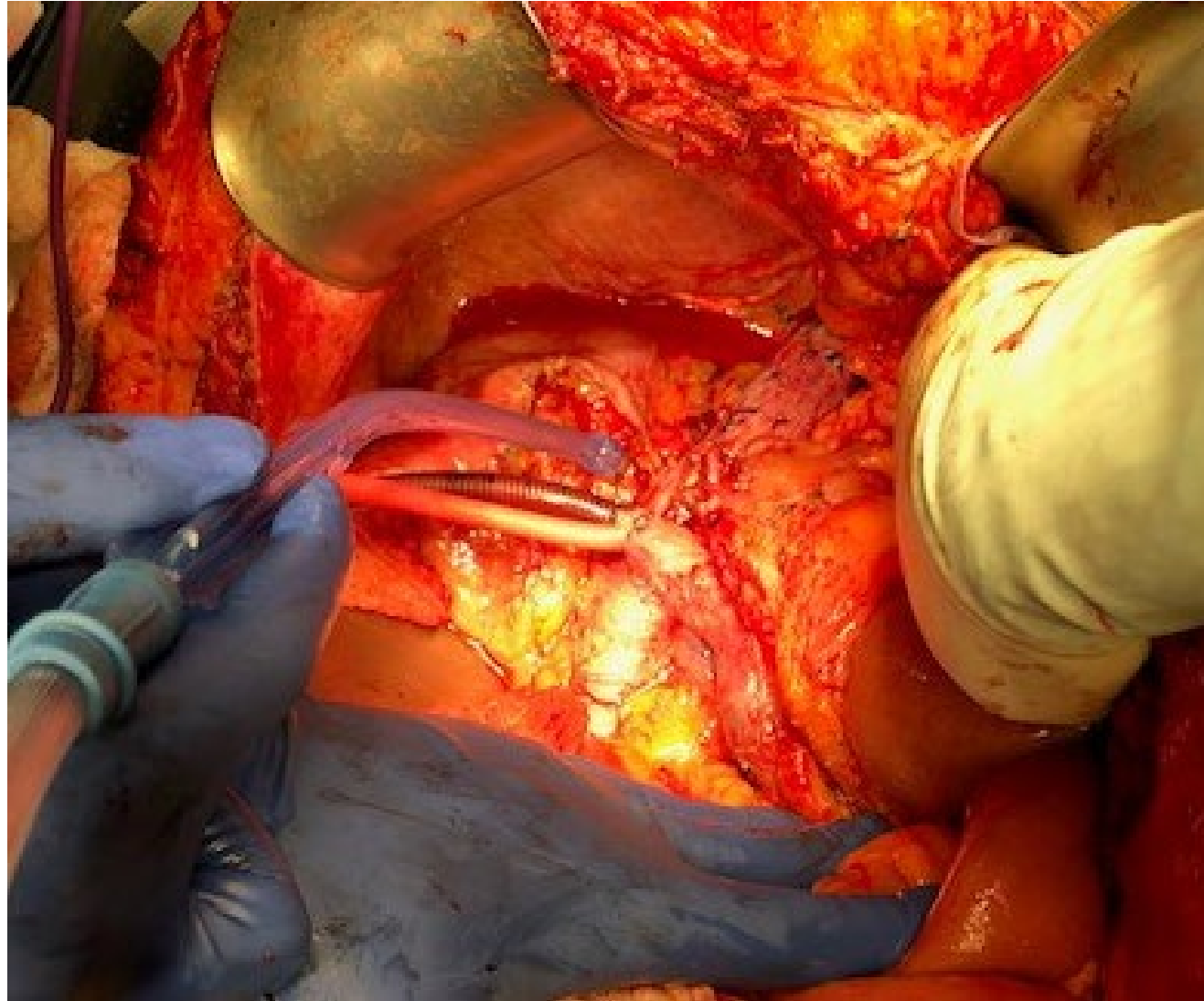
PART 4: DISTAL COMMON DUCT, RESECTION MARGIN:  
**CHOLANGIOCARCINOMA**, MODERATELY DIFFERENTIATED

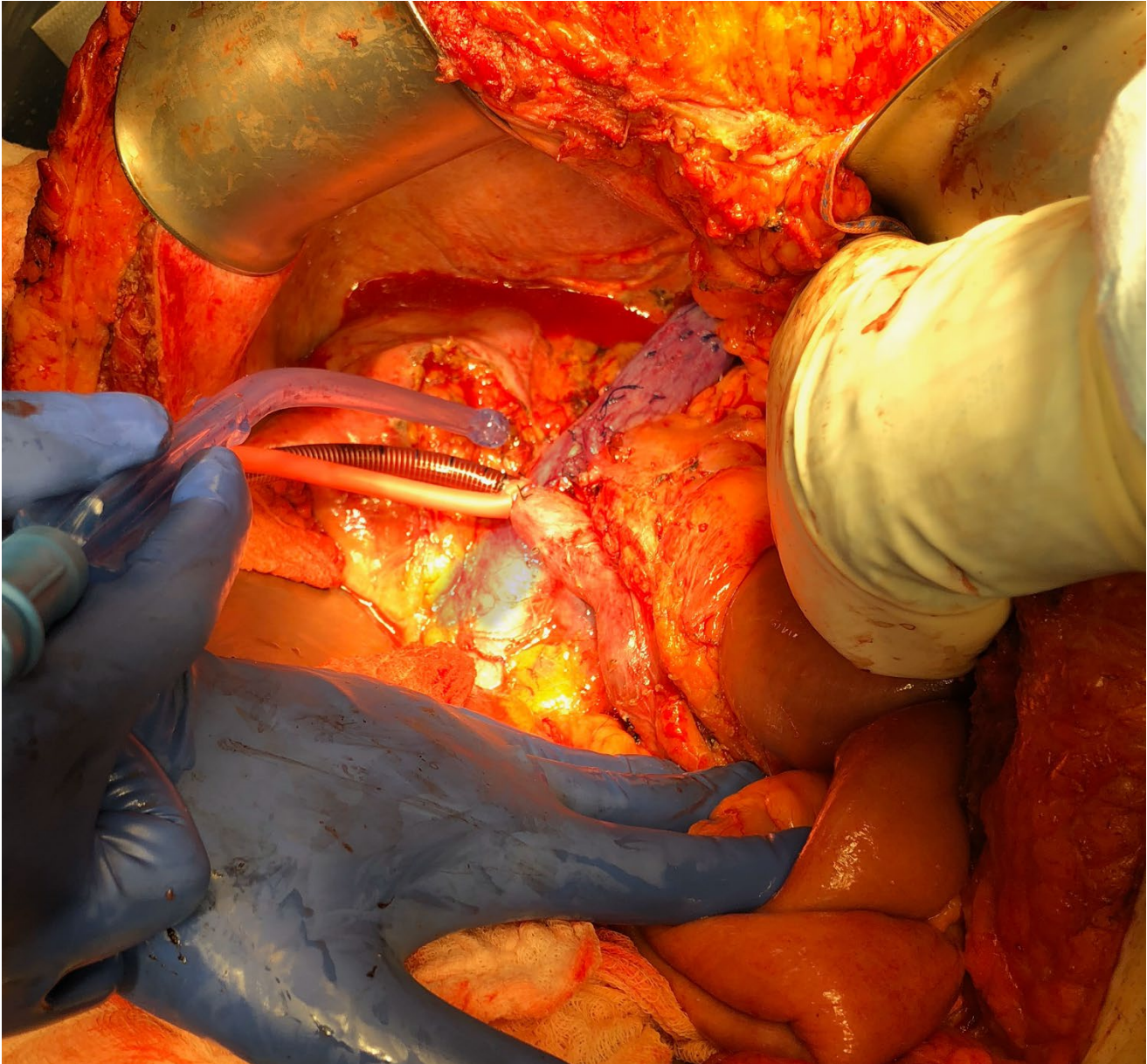


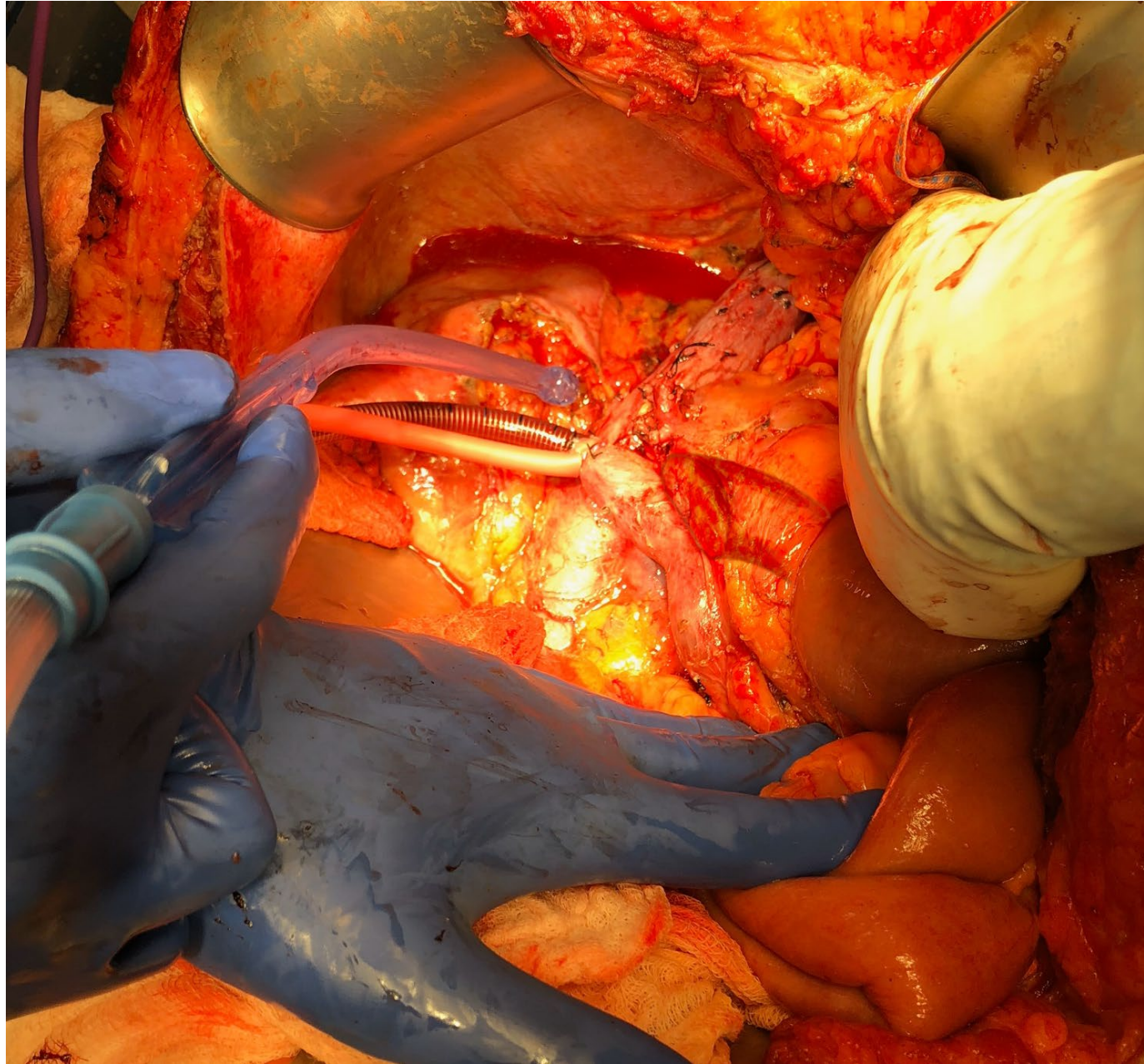


Copyright © 2004, Elsevier.

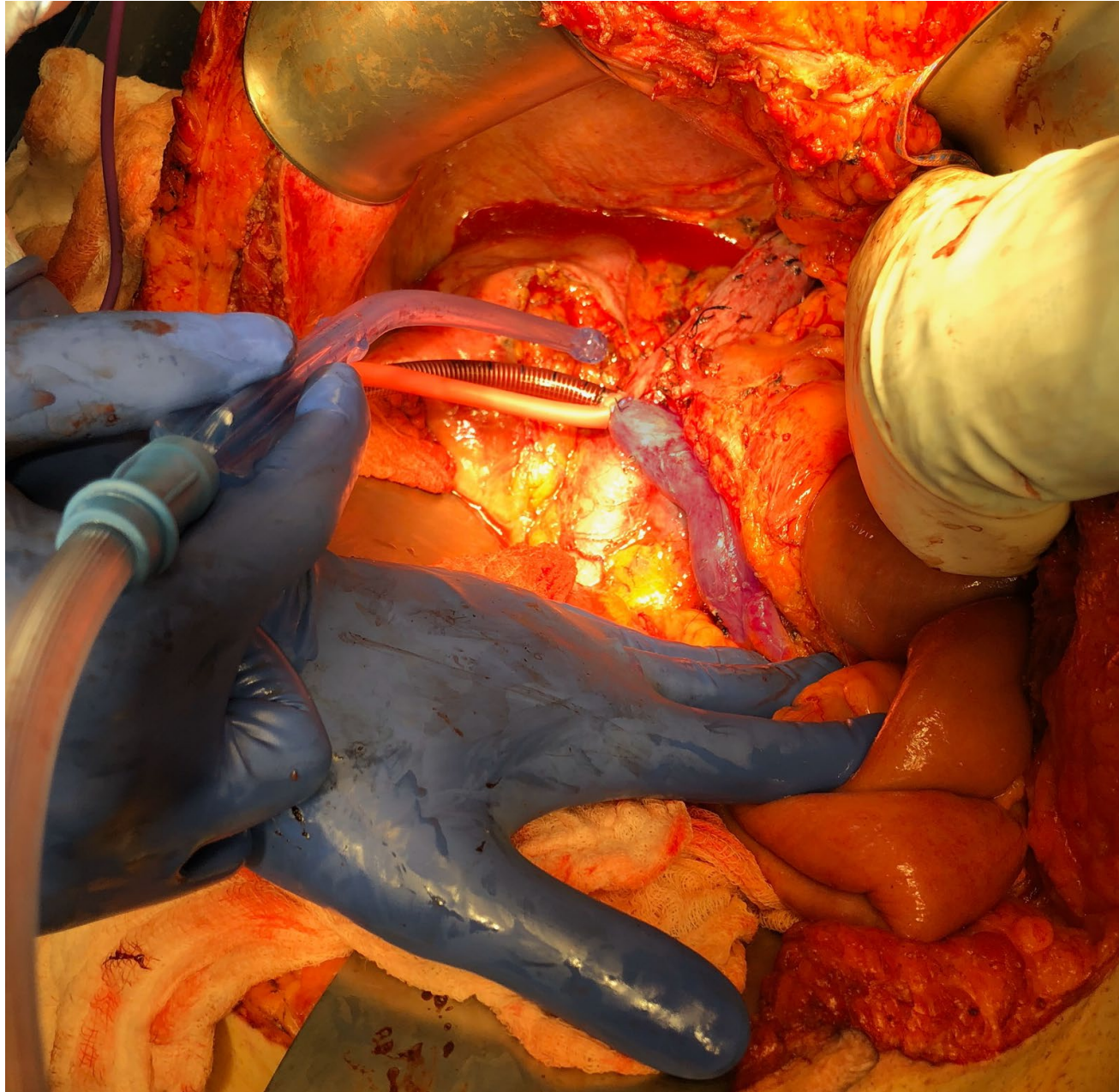




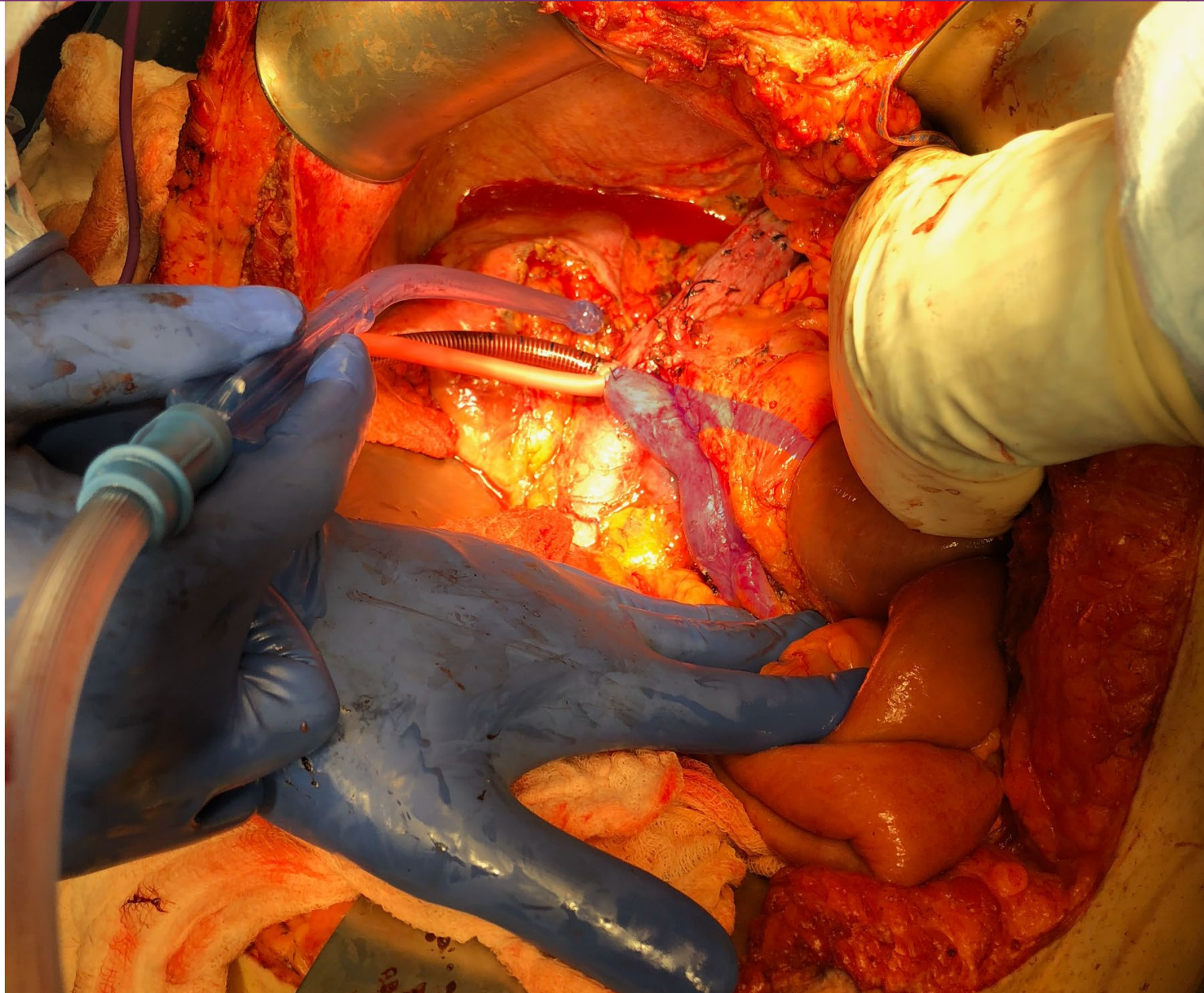


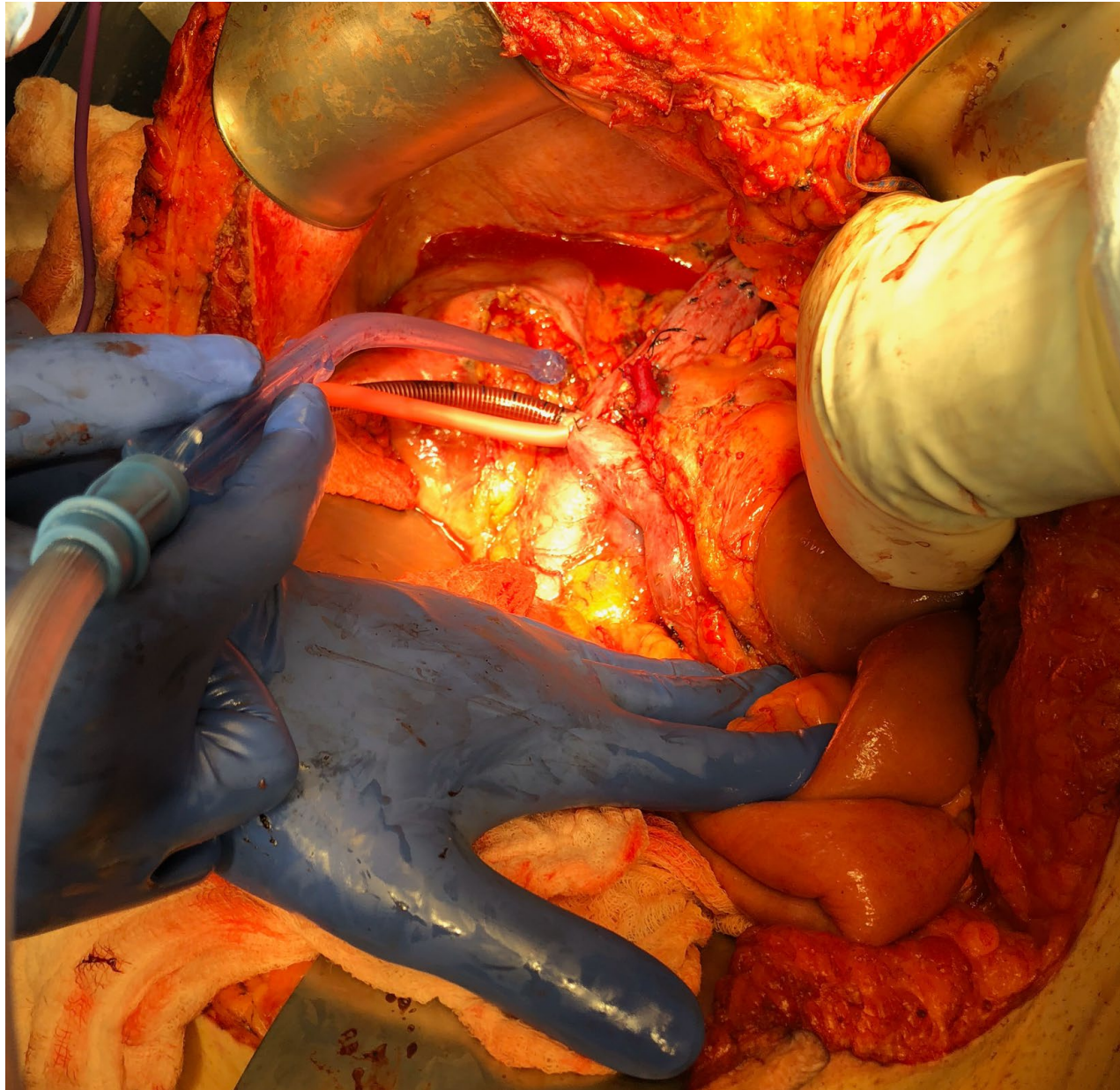


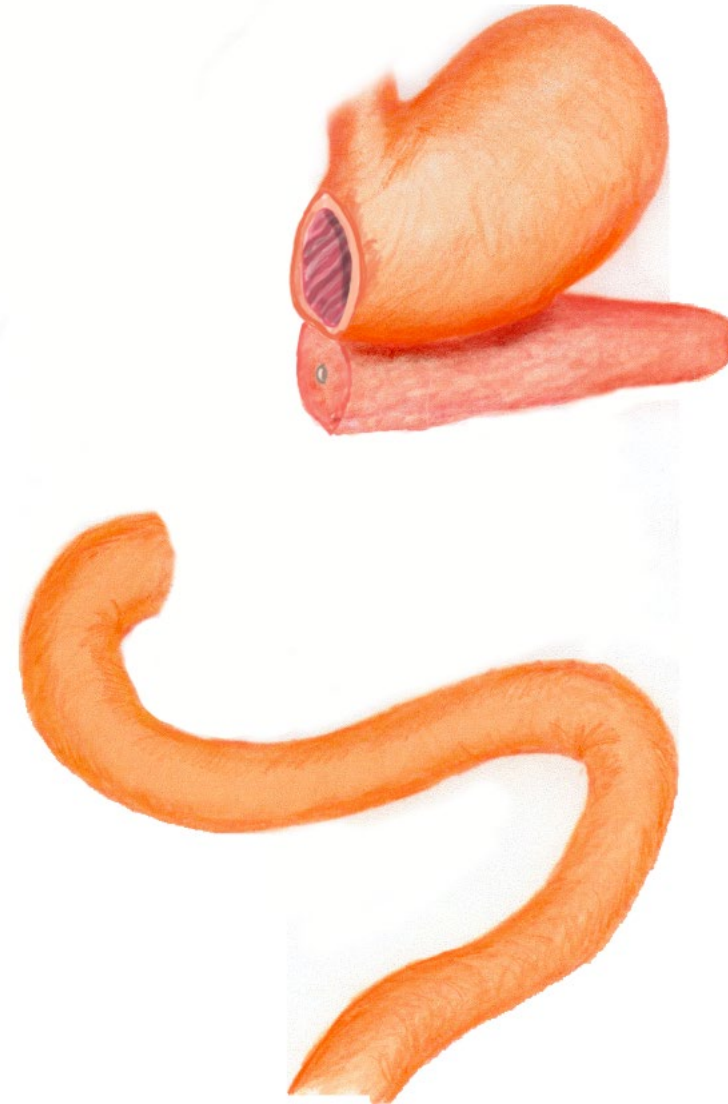


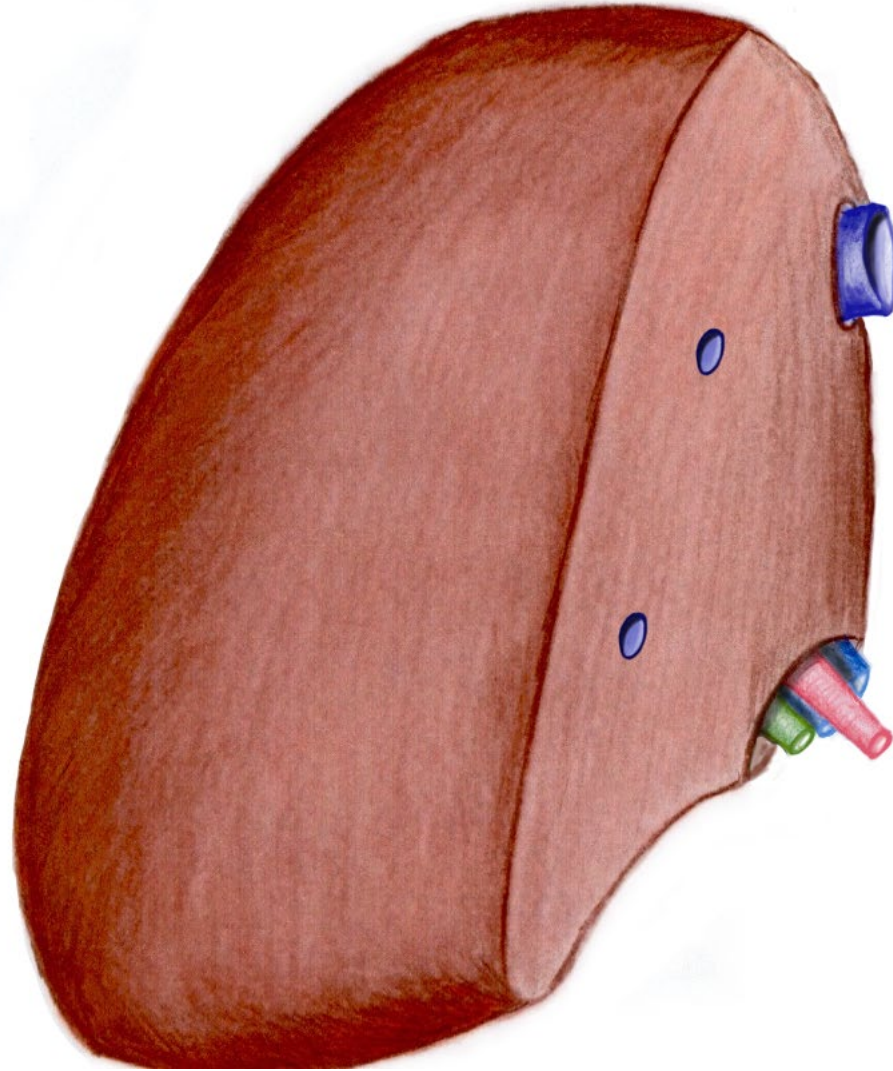


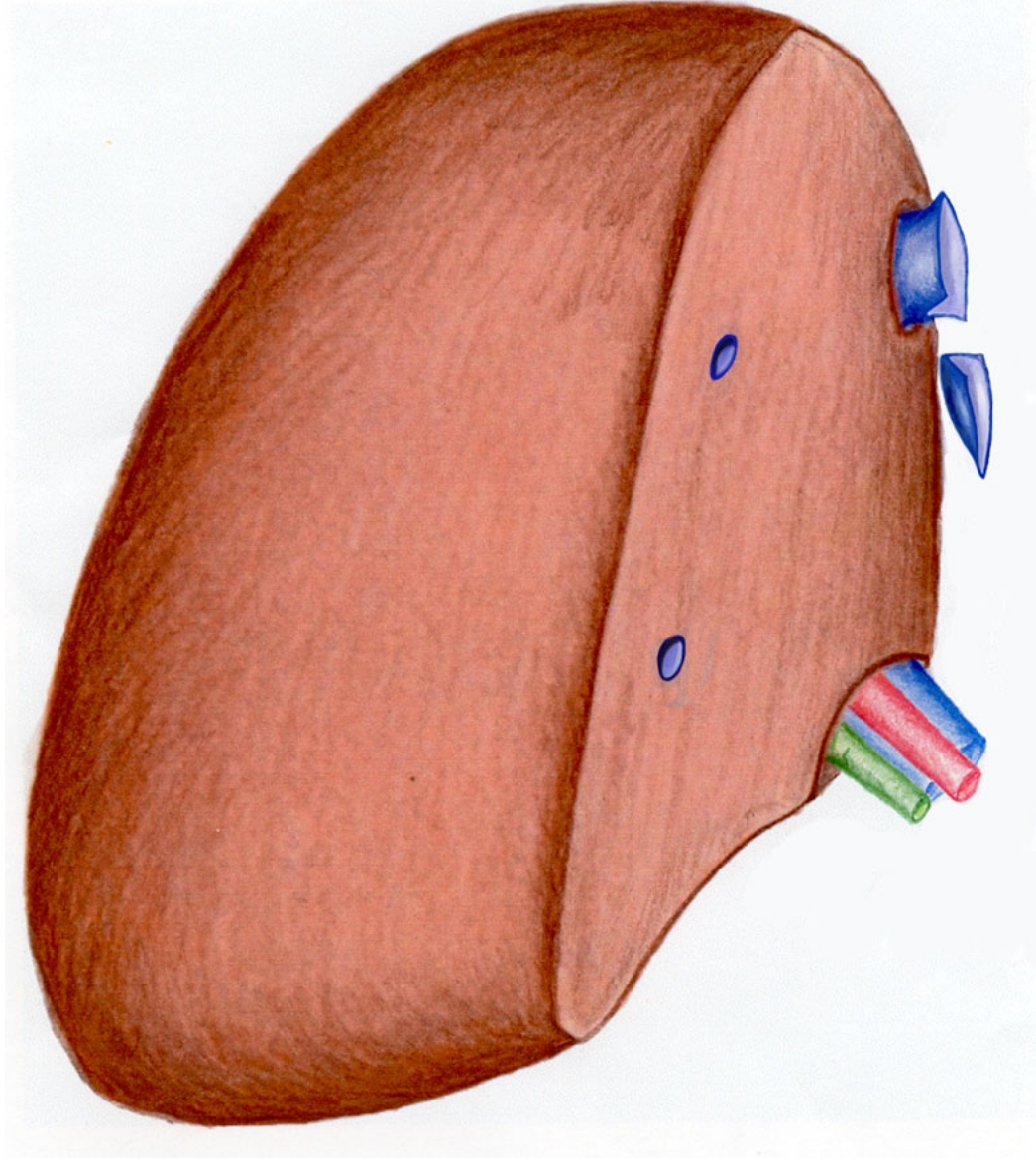
# Hilar Cholangiocarcinoma

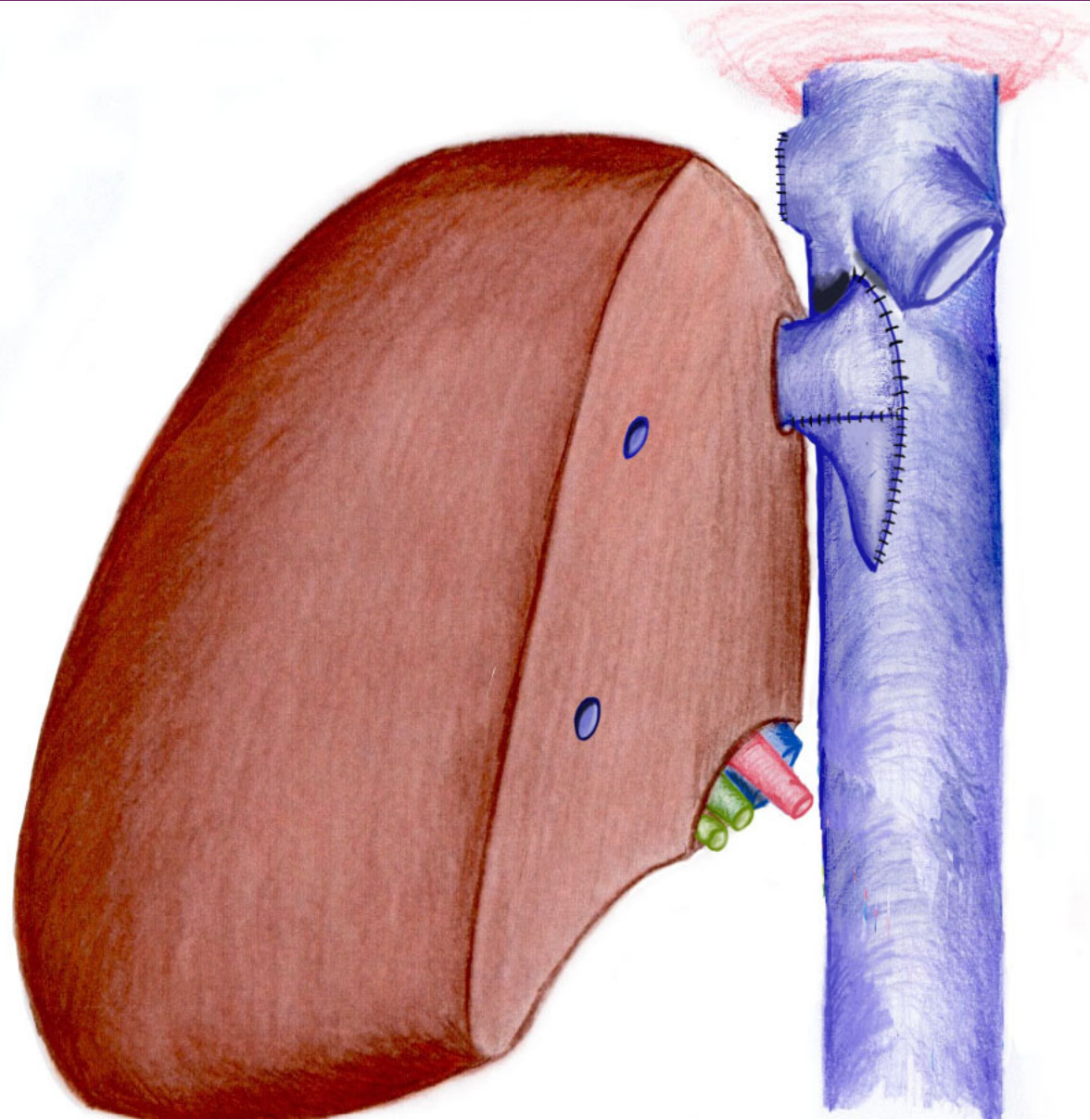


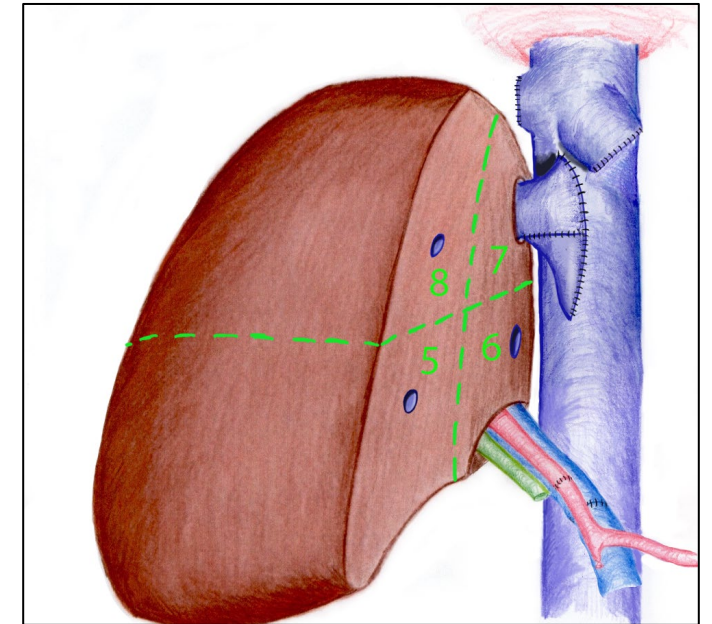
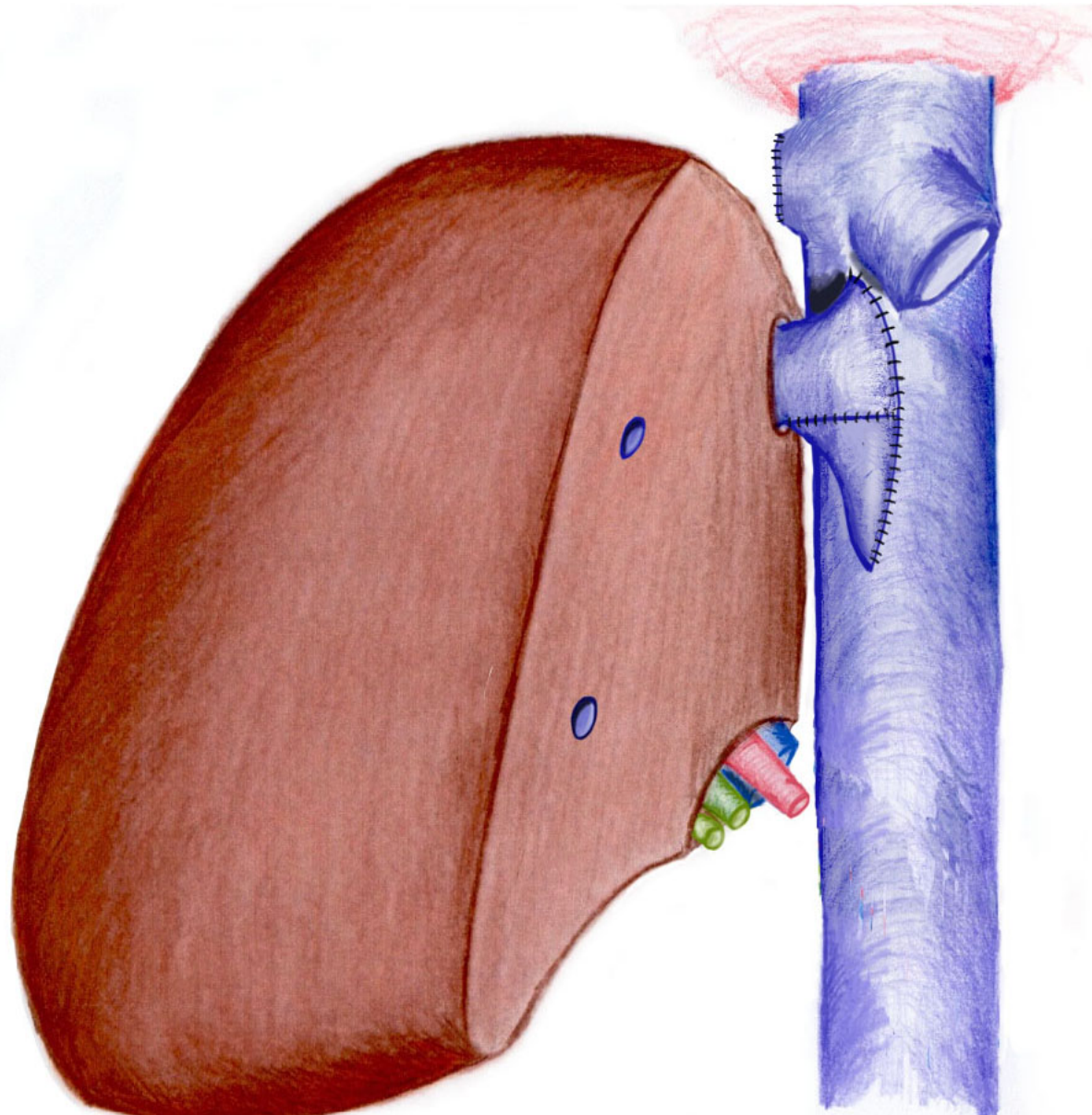








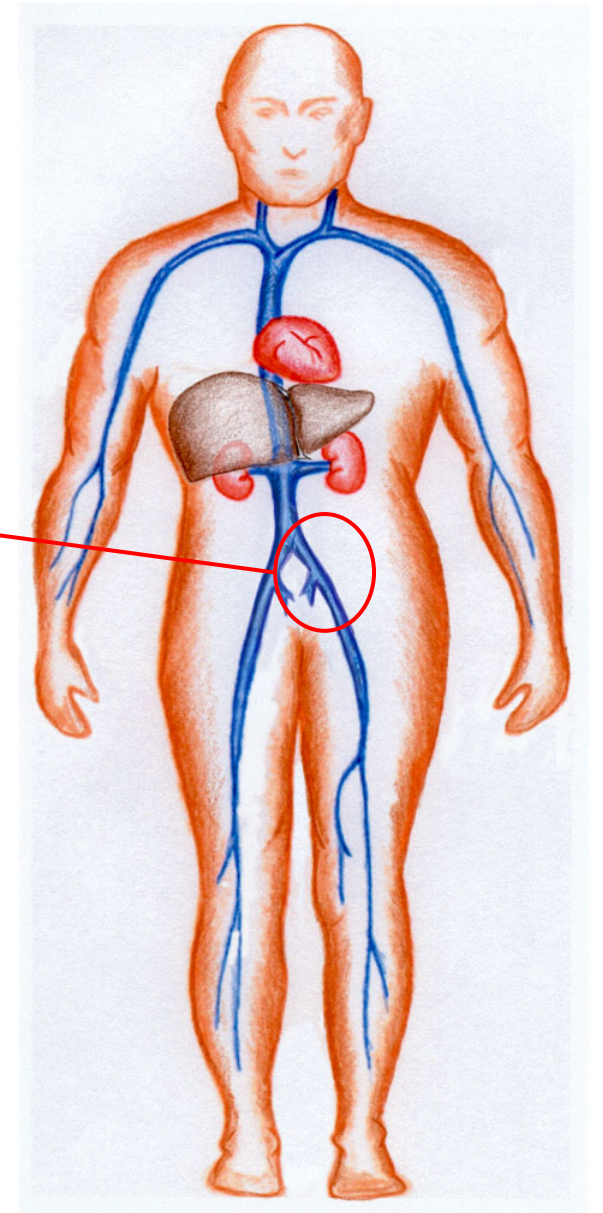
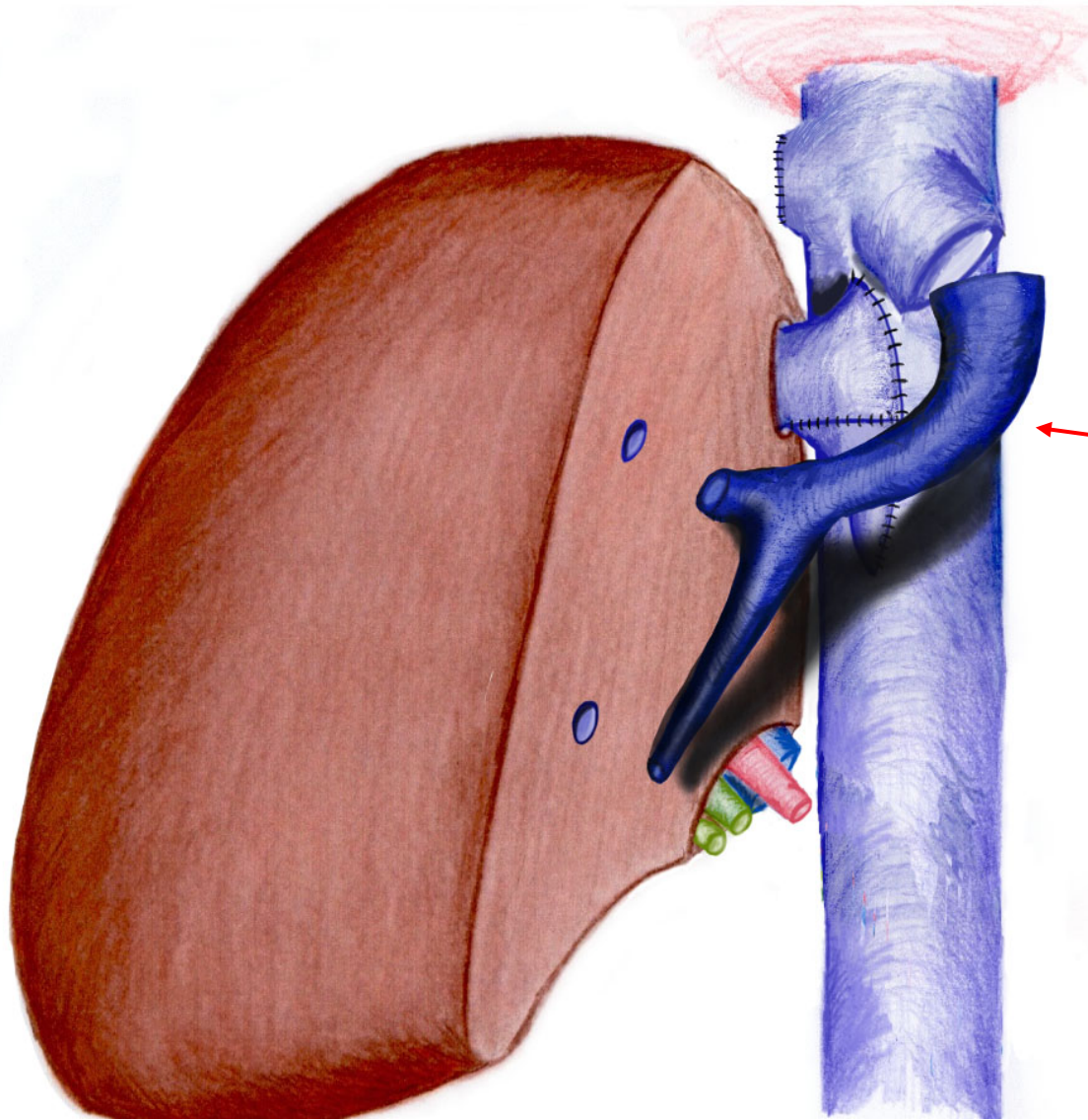


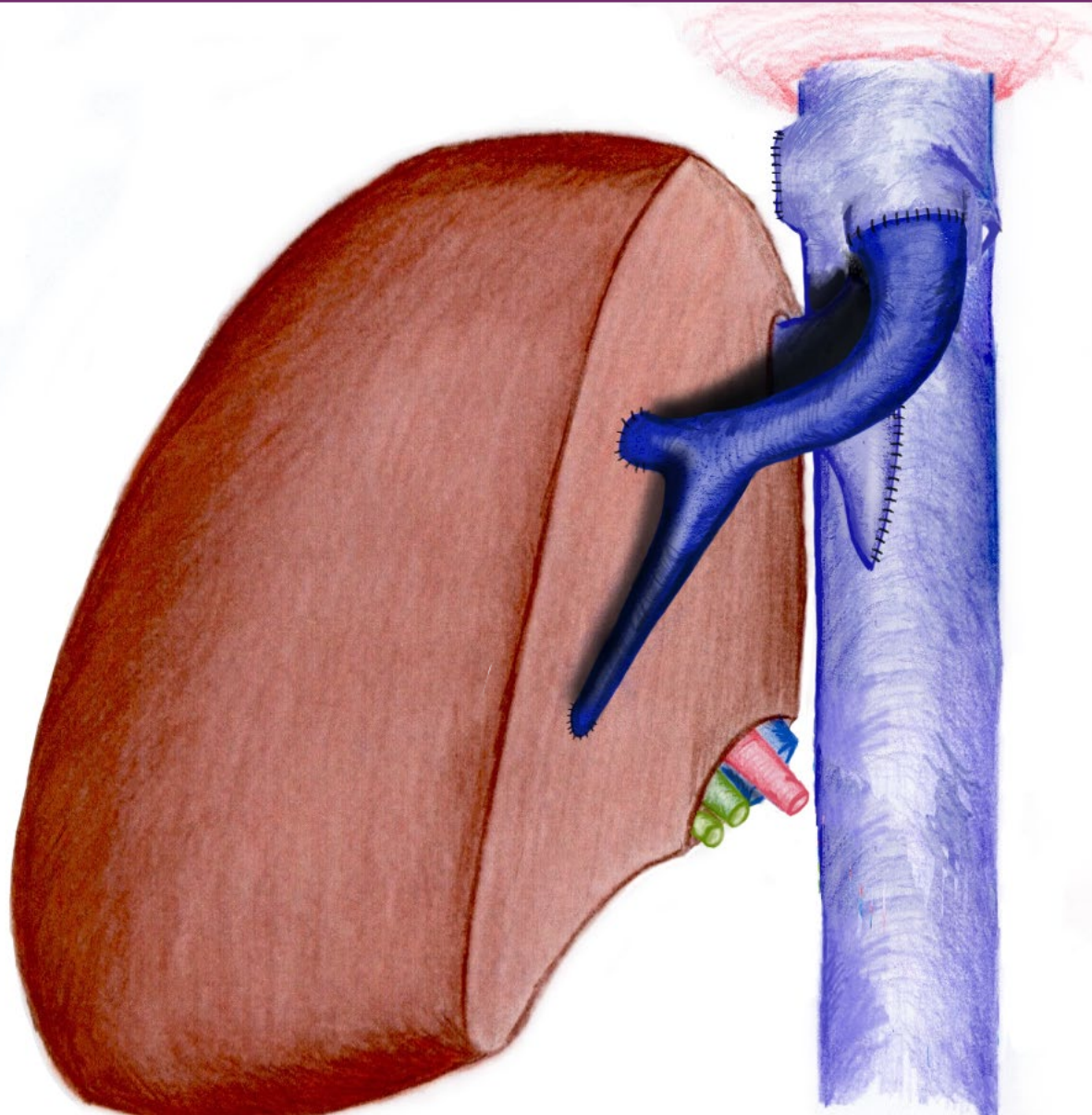


RHV to cava  
Segment 5/8 veins to M/L  
RPV to MPV  
RHA to CHA  
2 ducts to roux

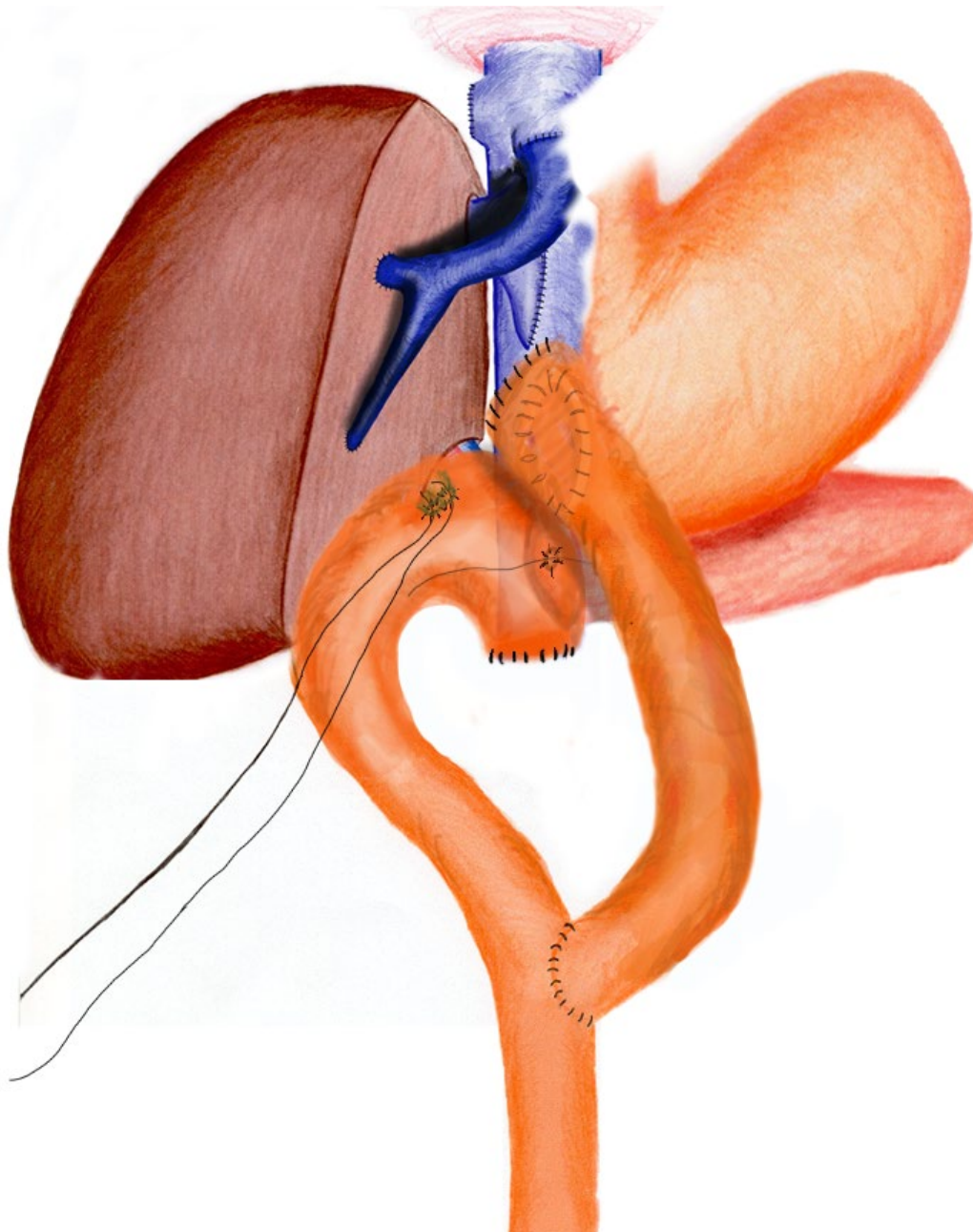


# Hilar Cholangiocarcinoma

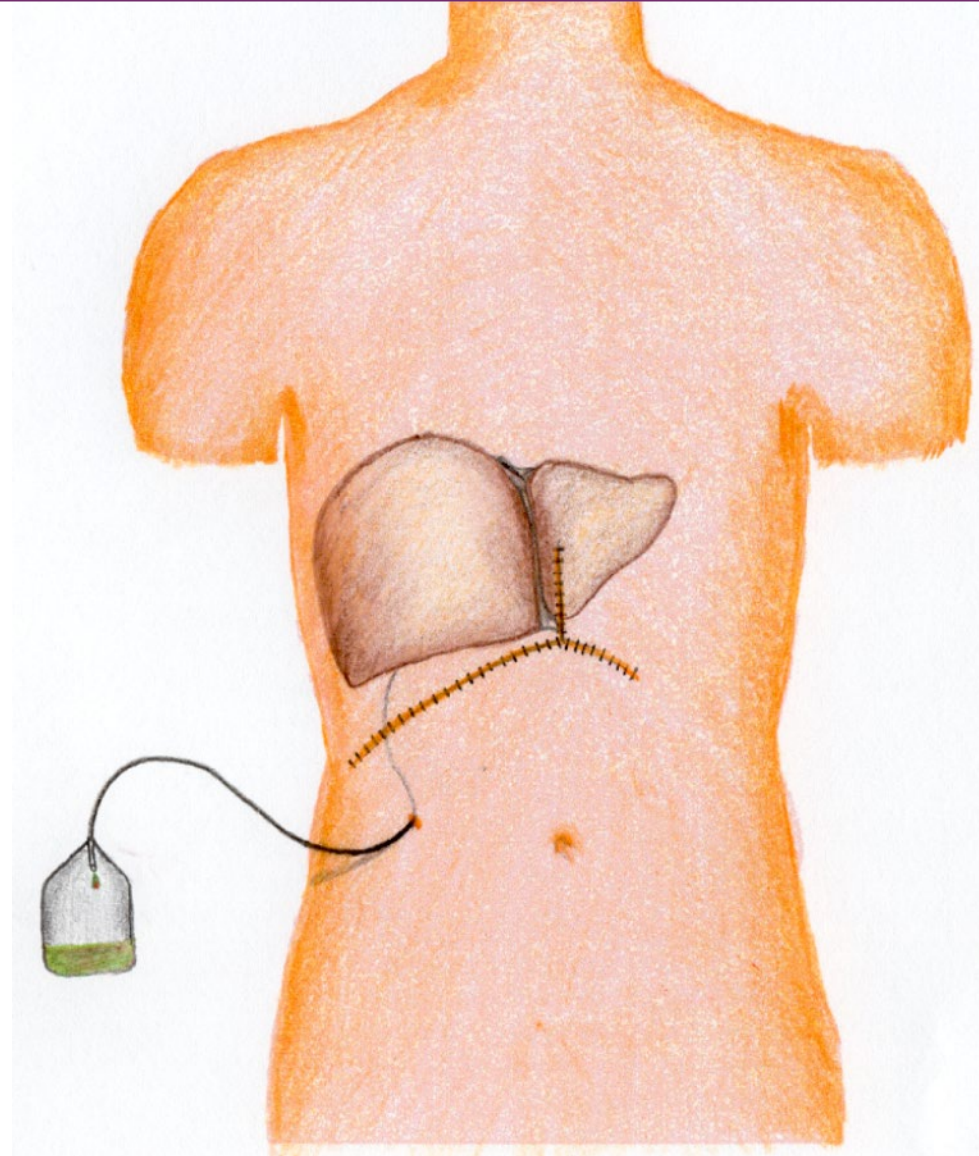




RHV to cava  
Segment 5/8 veins to M/L  
RPV to MPV  
RHA to CHA  
2 ducts to roux



RHV to cava  
Segment 5/8 veins to M/L  
RPV to MPV  
RHA to CHA  
2 ducts to roux



# Tube Cholangiogram



Total time 16h39

Flow Rate: Graft weight:	915 gm
Portal vein flow:	2.3 L/min
Hepatic artery flow:	160 ml/min
Portal pressure:	14 mmHg
Jump graft flow:	0.57 L/min

PRBC 0

FFP 0

Plt 0

Cryo 0

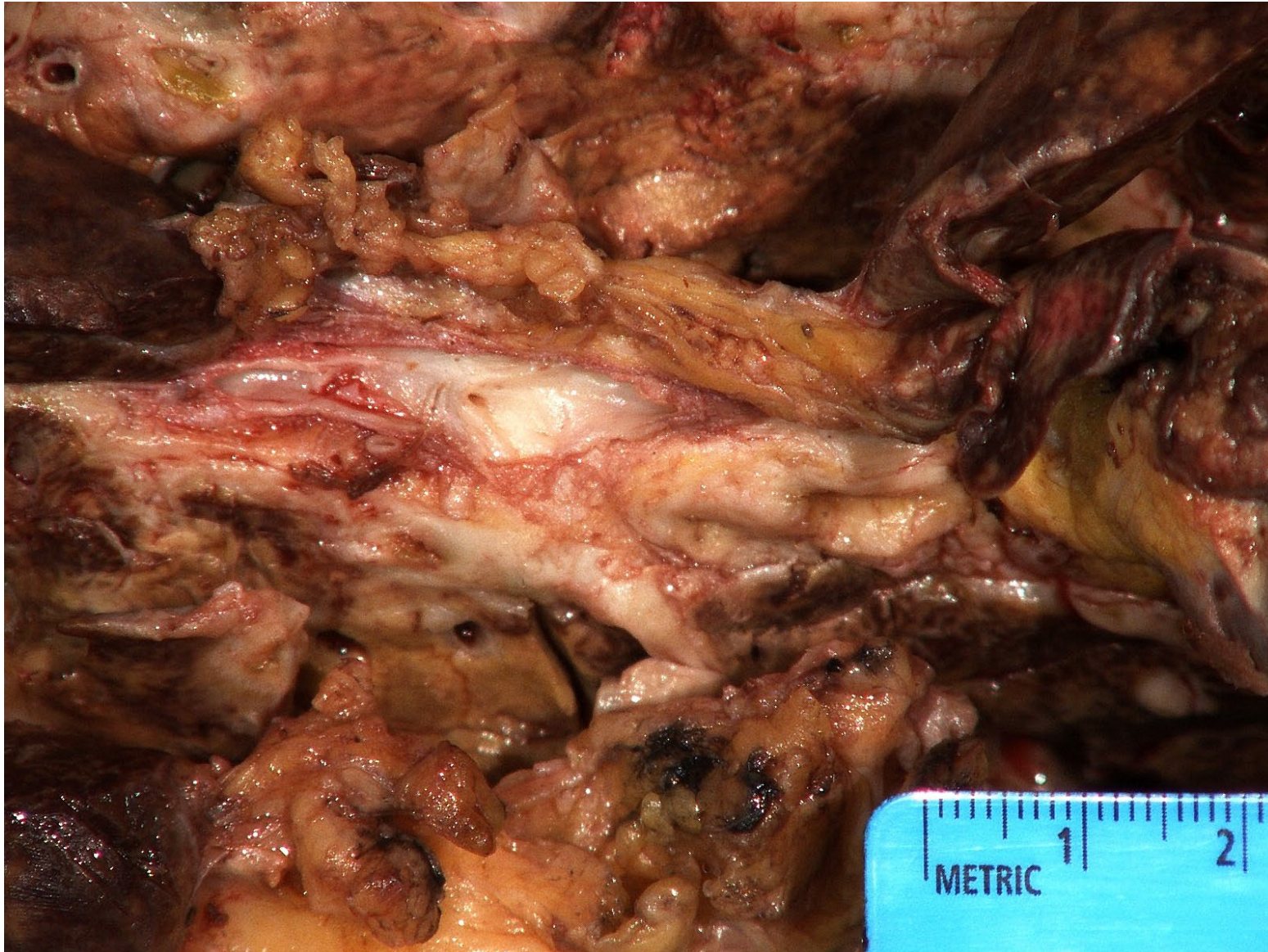
## FINAL PATHOLOGY:

NATIVE LIVER, ORTHOTOPIC TRANSPLANT PROCEDURE:

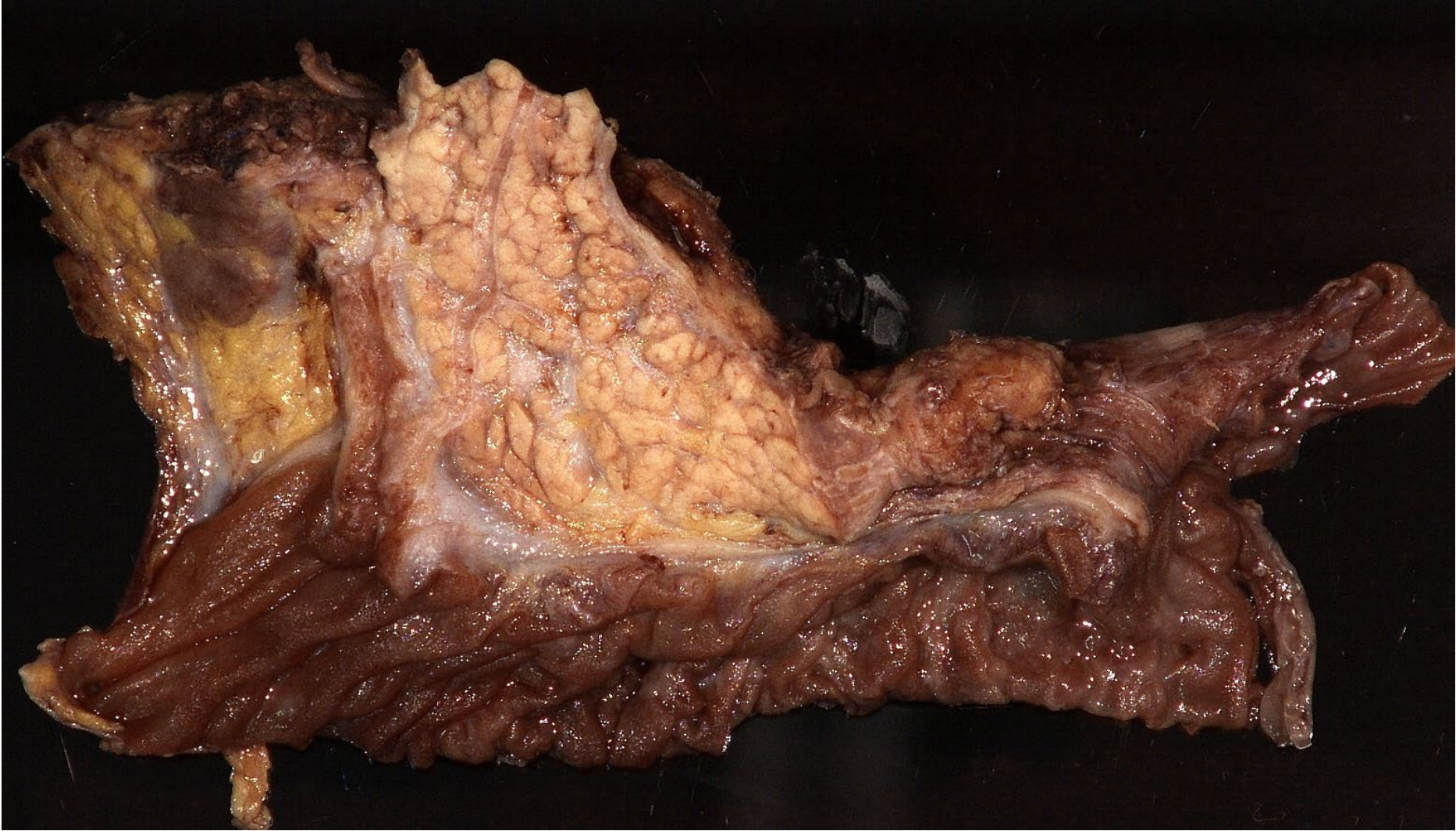
- A. CHOLANGIOCARCINOMA, 2.7 CM, INVOLVING THE COMMON, RIGHT AND LEFT HEPATIC DUCTS.
- B. PORTAL VEIN, HEPATIC VEIN AND HEPATIC ARTERY WITH NO EVIDENCE OF TUMOR.
- C. NO LYMPHOVASCULAR INVASION IS IDENTIFIED.
- D. TWO LYMPH NODE WITH NO TUMOR SEEN (0/2).
- E. PATHOLOGIC TNM STAGING: pT2b N0 MX.

PORTIONS OF STOMACH, DUODENUM AND PANCREAS, WHIPPLE RESECTION PROCEDURE:

- A. CHOLANGIOCARCINOMA IN COMMON BILE DUCT STUMP ATTACHED TO DUODENUM.
- B. MILD CHRONIC PANCREATITIS: NO TUMOR SEEN.
- C. DUODENAL, AMPULLARY AND GASTRIC MUCOSA: NO TUMOR SEEN.
- D. FIFTEEN LYMPH NODES WITH NO TUMOR SEEN (0/15).







Post-LDLT 12/18/17

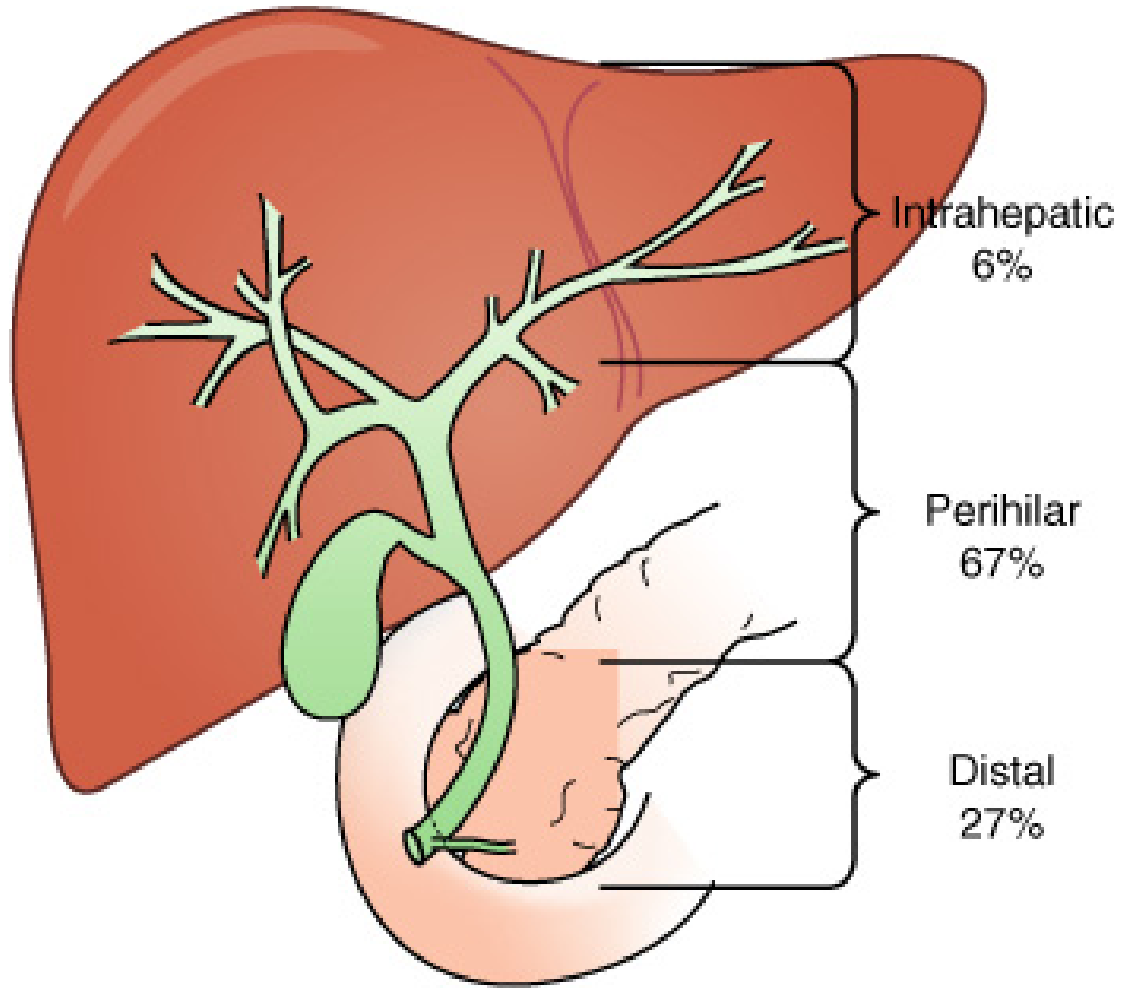
Almost 4 years post-OLT

No recurrence

Ca19-9 normal



# Distribution of Cholangiocarcinoma

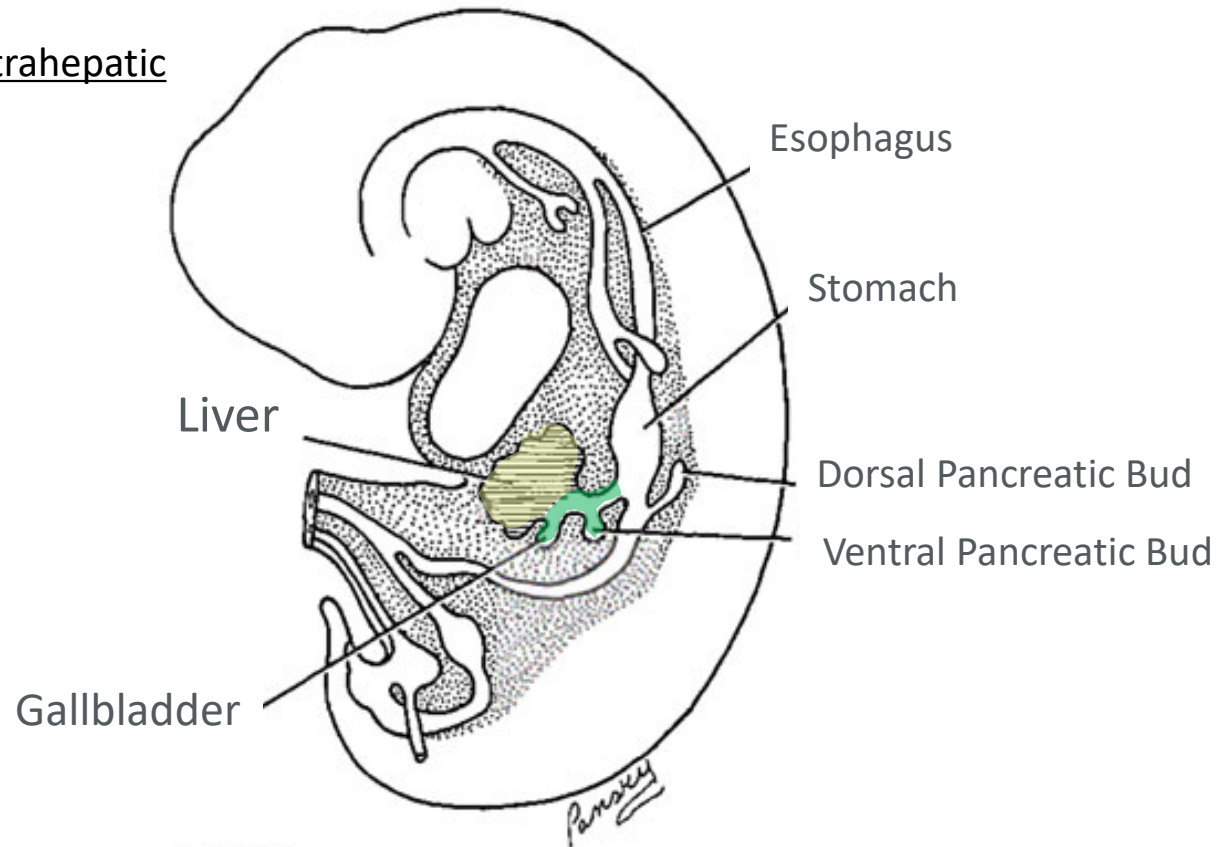


Copyright © 2004, Elsevier.

# Bile Duct Embryology

Ventral Foregut Endoderm develops two protrusions:

- **cranial part** leads to the formation of the intrahepatic bile ducts
- **caudal part** generates the extrahepatic biliary tree



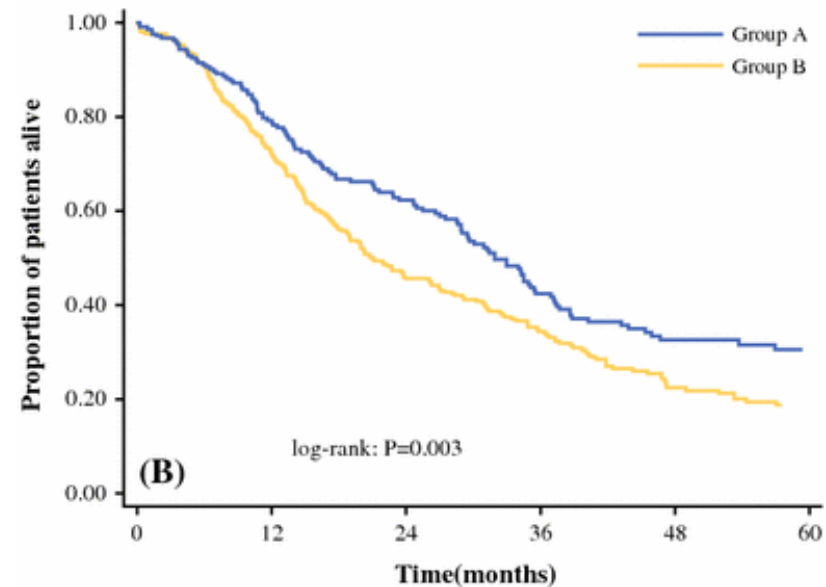
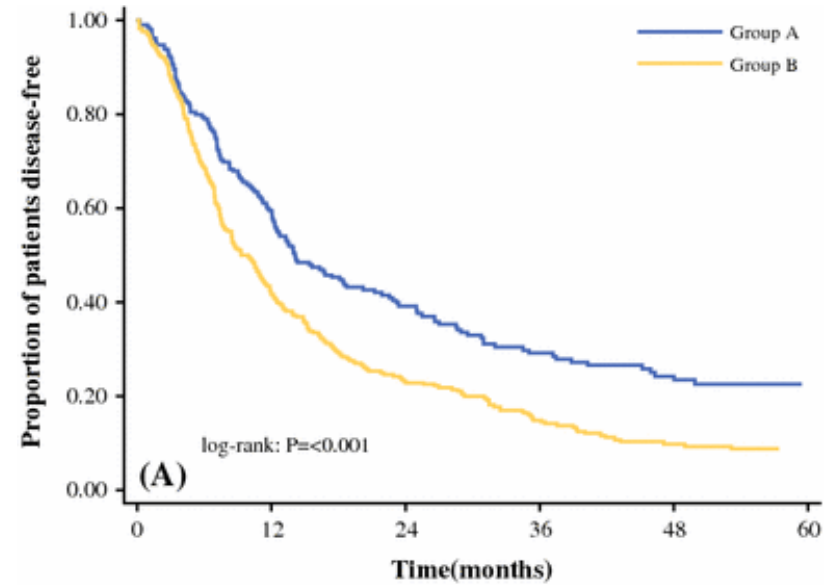
DAY 30  
Sagittal section

# Intrahepatic Cholangiocarcinoma

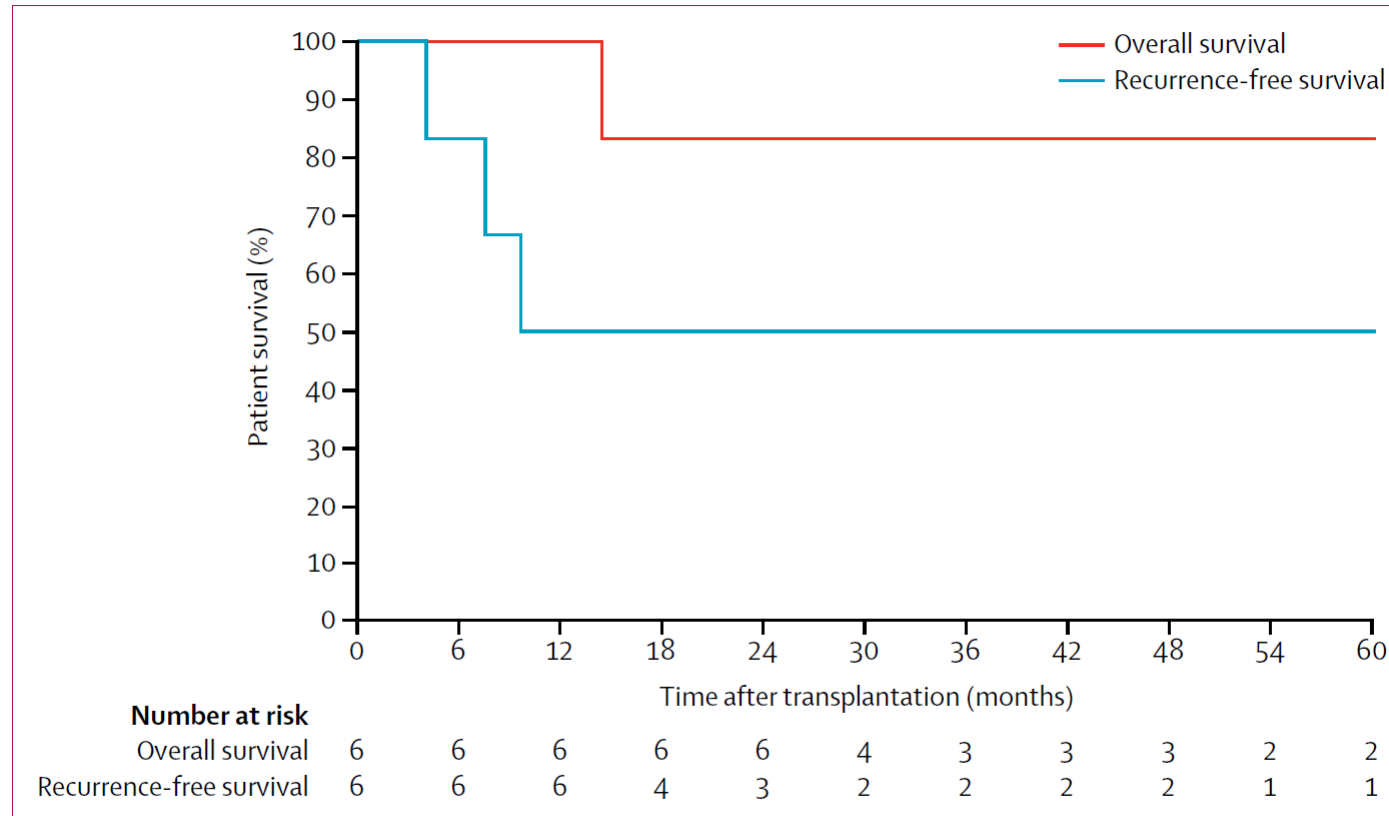
Intrahepatic CCA after surgery resection

- 550 patients
- Multicenter

60% of those who recurred, recurred only in the liver



# Intrahepatic Cholangiocarcinoma



**Figure 3:** Cumulative overall and recurrence-free survival after liver transplantation for intrahepatic cholangiocarcinoma

# Intrahepatic Cholangiocarcinoma—UPMC Protocol

## A. *Neoadjuvant Chemotherapy*

Gemcitabine 1000mg/m<sup>2</sup> and Cisplatin 25 mg/m<sup>2</sup> on days 1 and 8 of every 21 days for 6 months. (*ref. N Engl J Med 2010; 362:1273-81.*)

## A. *Locoregional Therapy*

Patients may benefit from locoregional therapy as a bridge to transplant. For smaller tumors (< 3 cm), consider percutaneous radiofrequency ablation, preferable at time of initial biopsy. For larger tumors or tumors inaccessible by RFA, consider transarterial chemoembolization (Gem/Cis or Gem/Oxaliplatin based). For centrally located tumors, consider external beam radiation. (*ref HepatoBiliary Surg Nutr 2017;6(2):105-116.*)

## A. *Exploratory Laparotomy (at time of scheduled living-donor recipient procedure)*

65 yo female with NASH cirrhosis

MRI: 4cm mass segment 5/6 3/5/19 c/w Cholangiocarcinoma

Started Gemcitabine/Cisplatin in May 2019

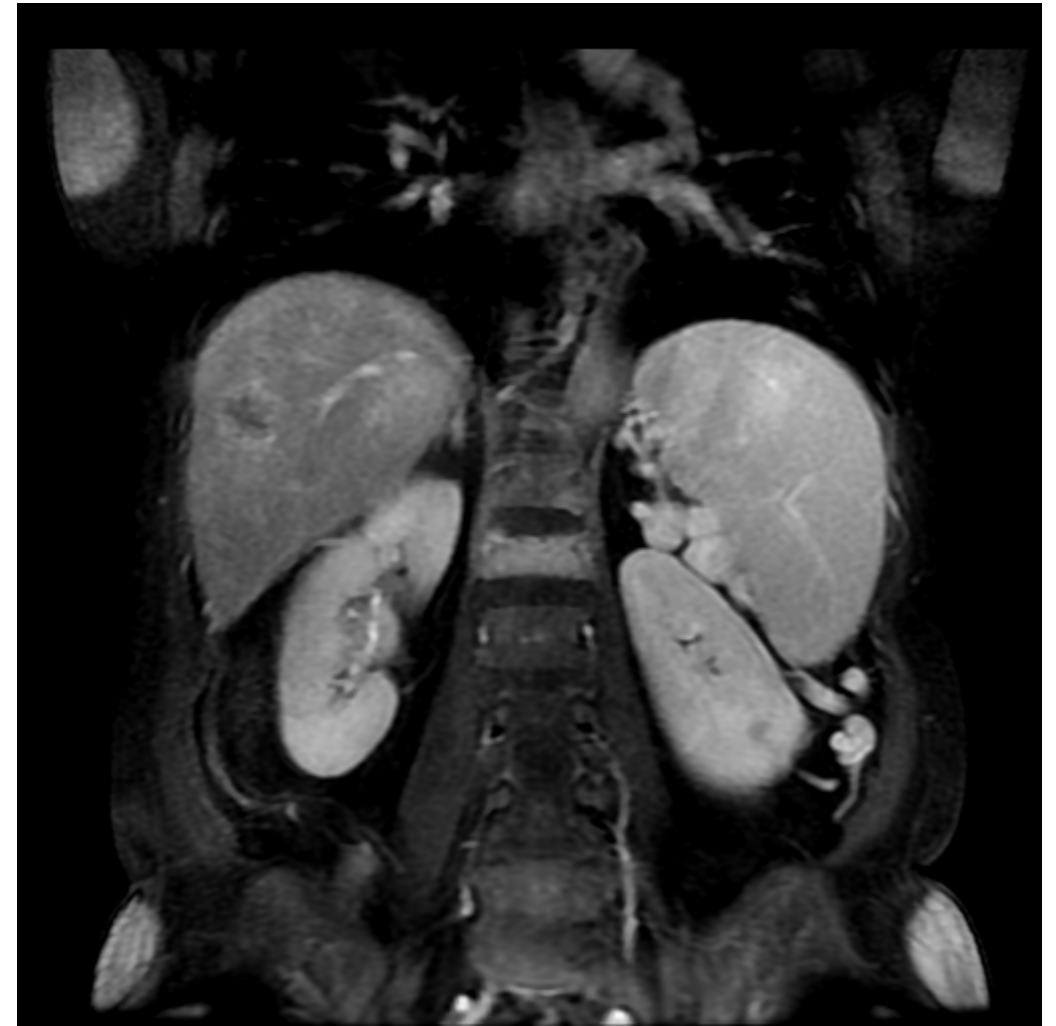
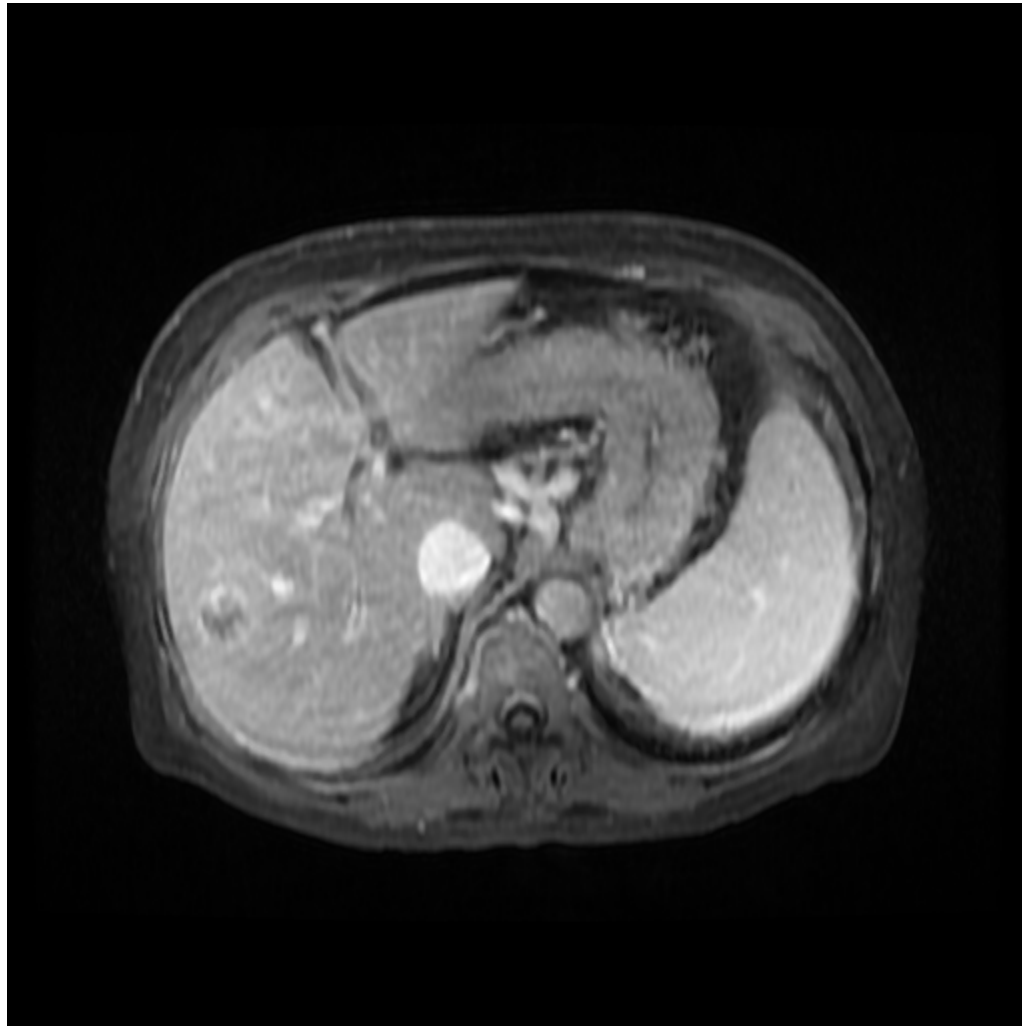
TACE in May 2019

Referred to UPMC for possible transplant

Negative workup for extrahepatic disease including negative bone scan

Presented to Committee October 2019



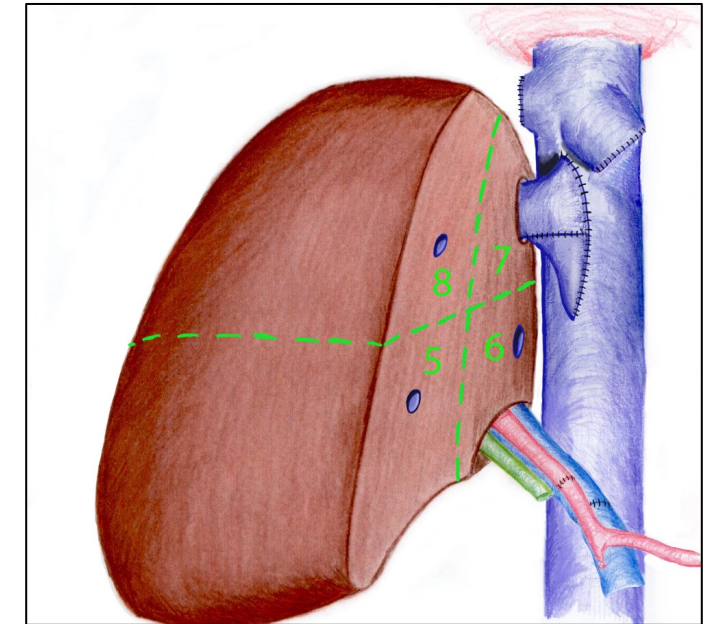
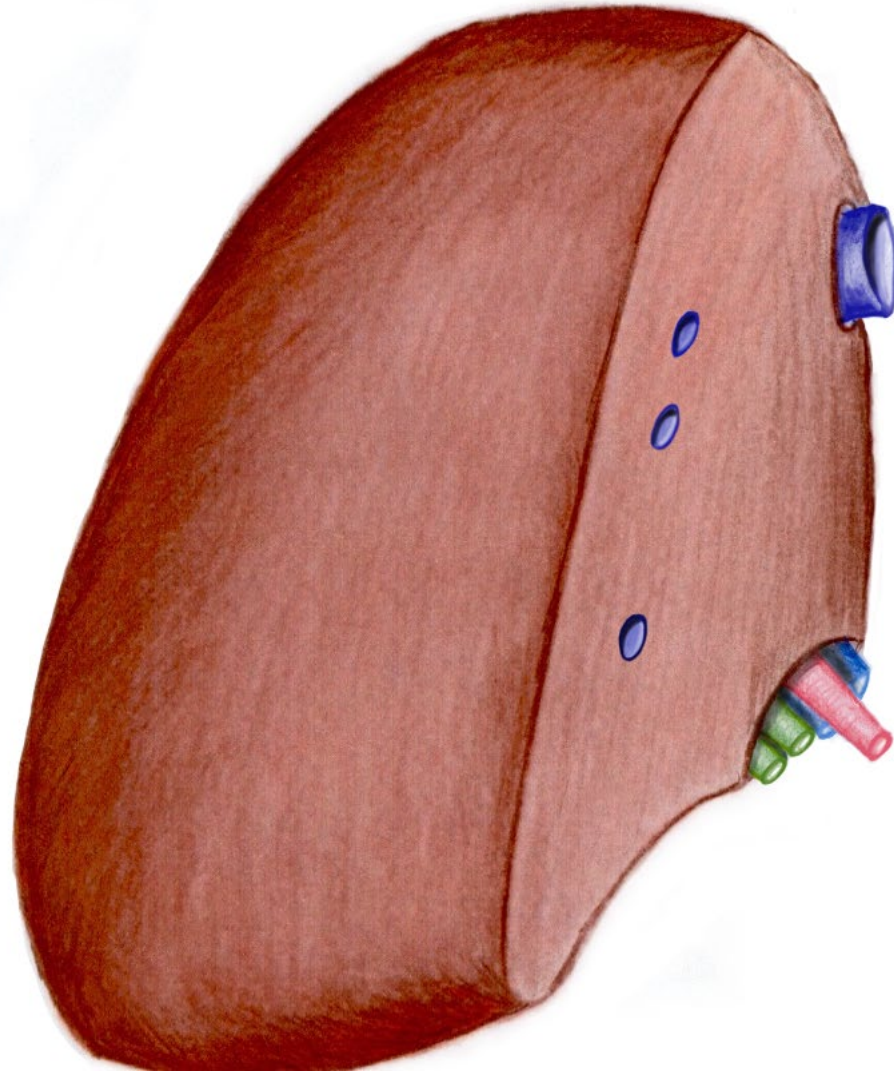


3.5 cm CCA in segment 5/6

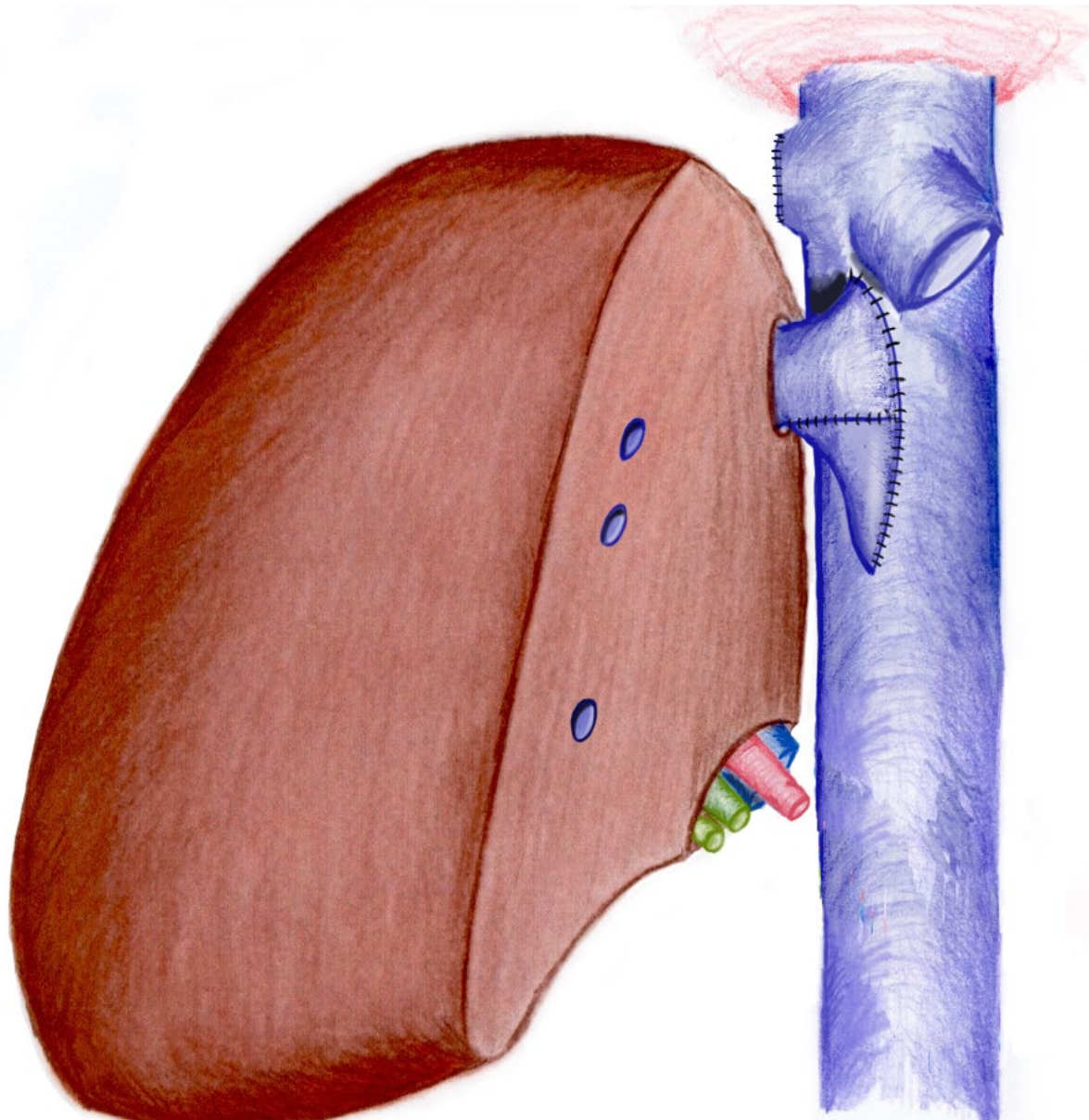
LDLT 11/1/19

Donor = son

Exploration first, no extrahepatic disease



Right Lobe  
RHV to cava  
Seg 5 and two seg 8 veins to LHV  
RPV  
Two ducts sewn separately with ext caths



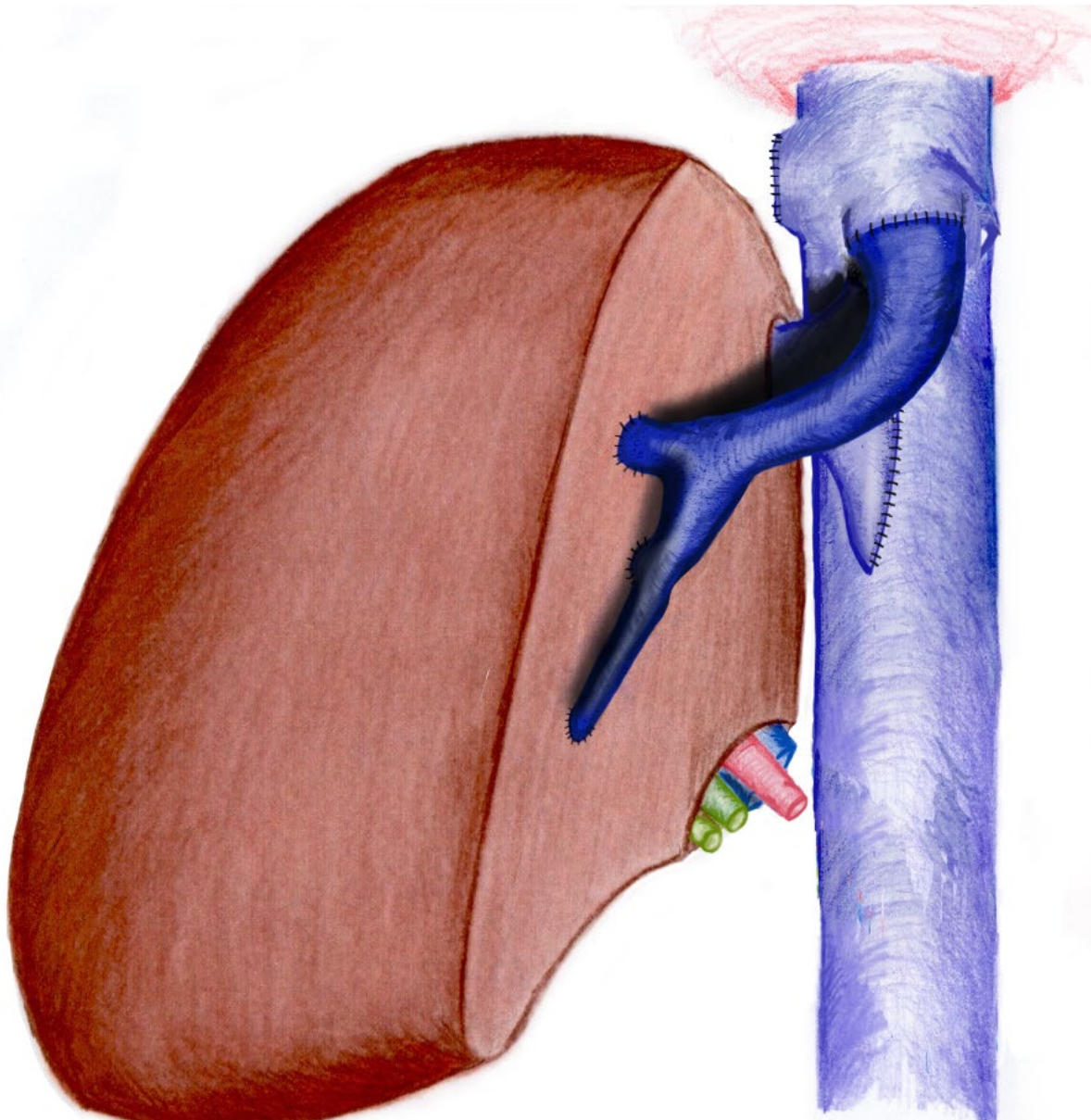
Right Lobe

RHV to cava

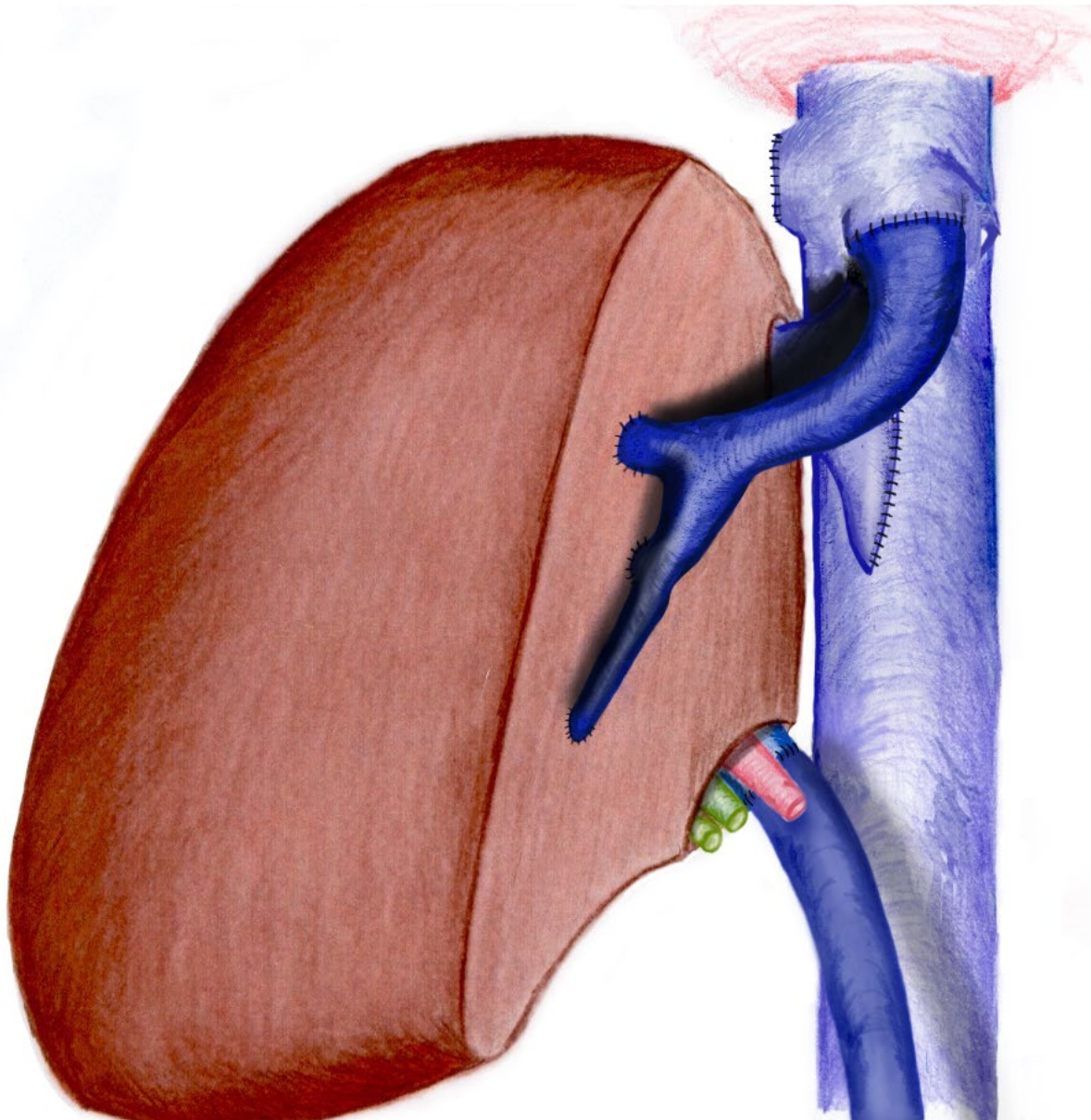
Seg 5 and two seg 8 veins to LHV

RPV to SMV jump graft

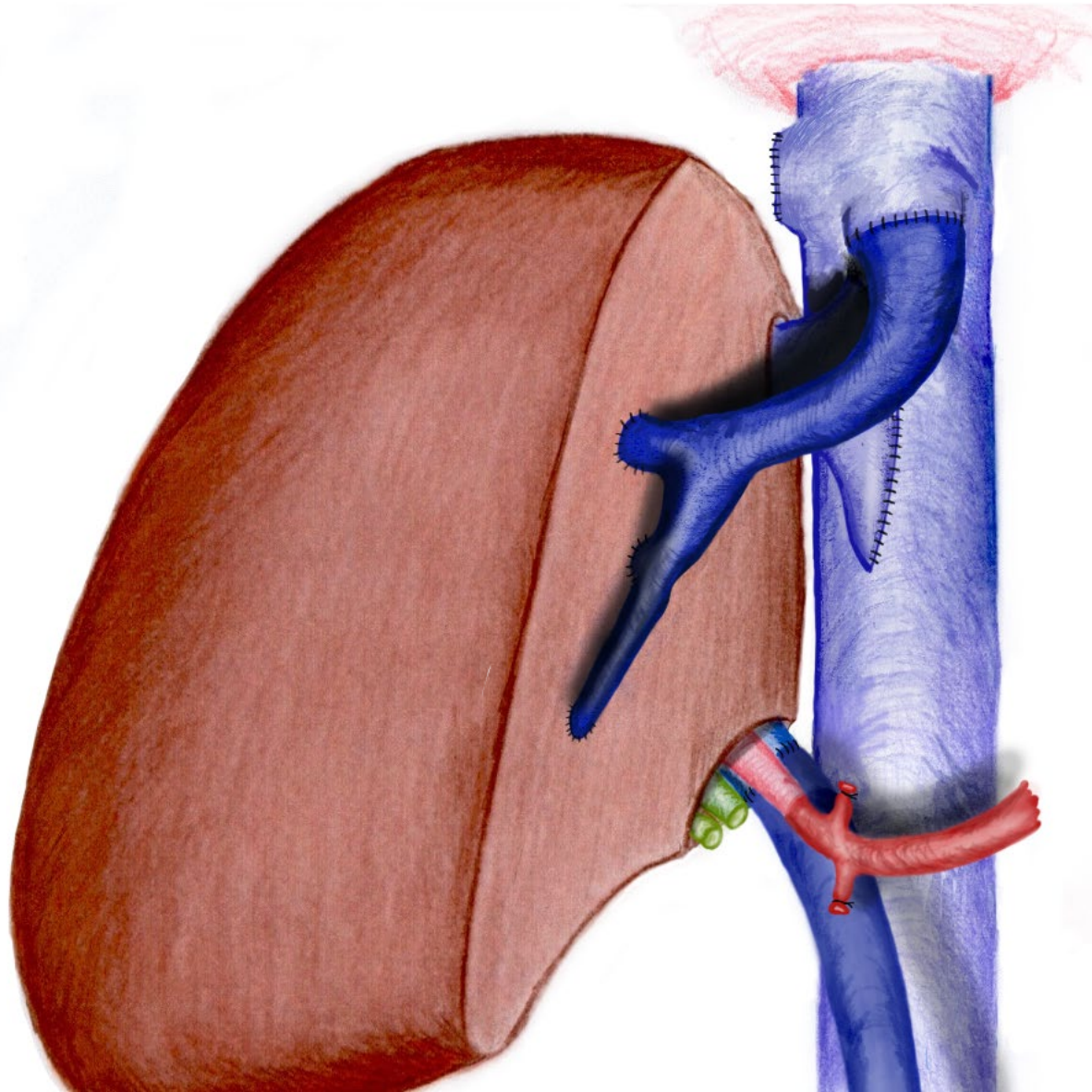
Two ducts sewn separately with ext caths



Right Lobe  
RHV to cava  
Seg 5 and two seg 8 veins to LHV  
RPV to SMV jump graft  
Two ducts sewn separately with ext caths



Right Lobe  
RHV to cava  
Seg 5 and two seg 8 veins to LHV  
RPV to SMV jump graft  
Two ducts sewn separately with ext caths



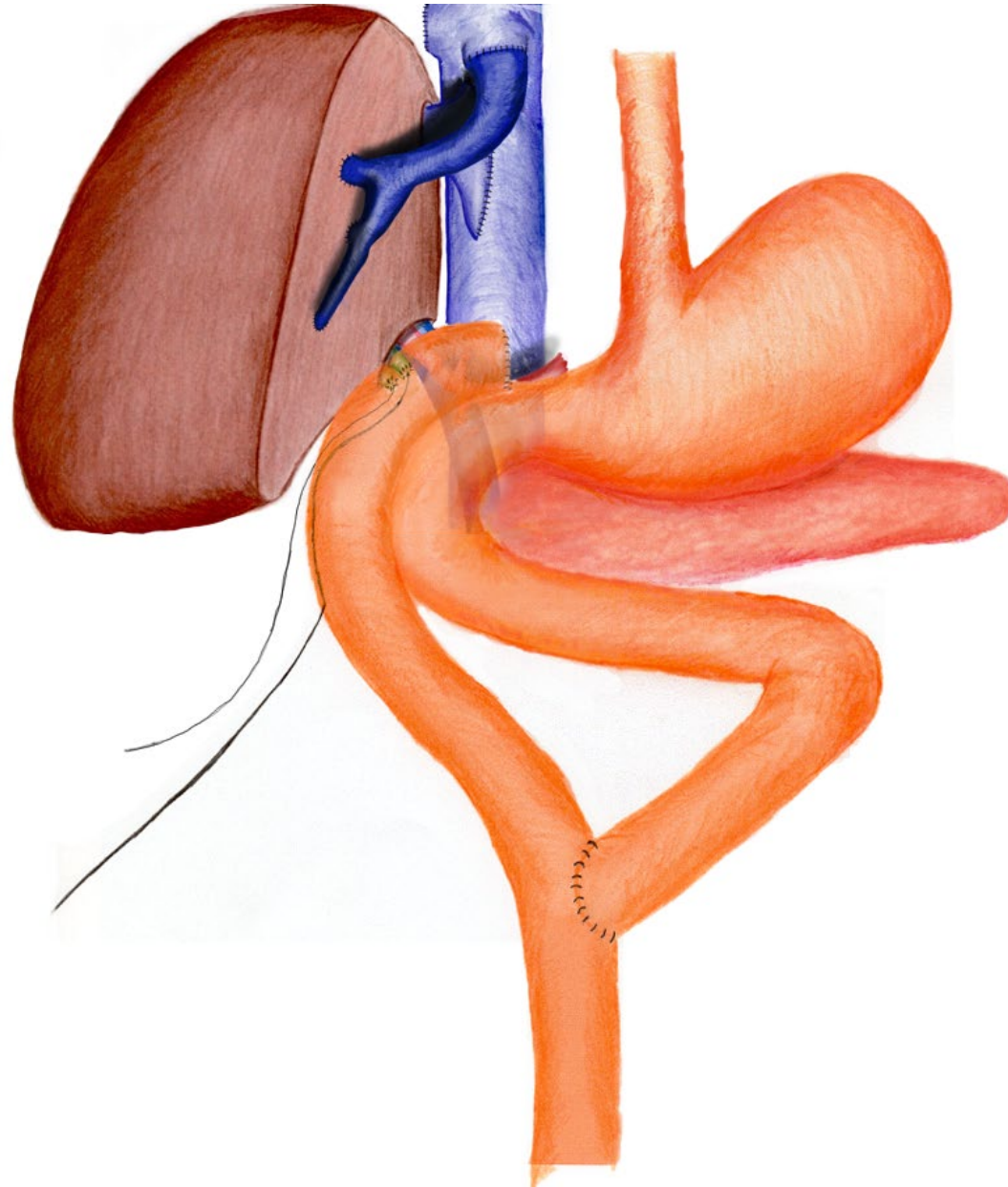
Right Lobe

RHV to cava

Seg 5 and two seg 8 veins to LHV

RPV to SMV jump graft

Two ducts sewn separately with ext caths



Right Lobe

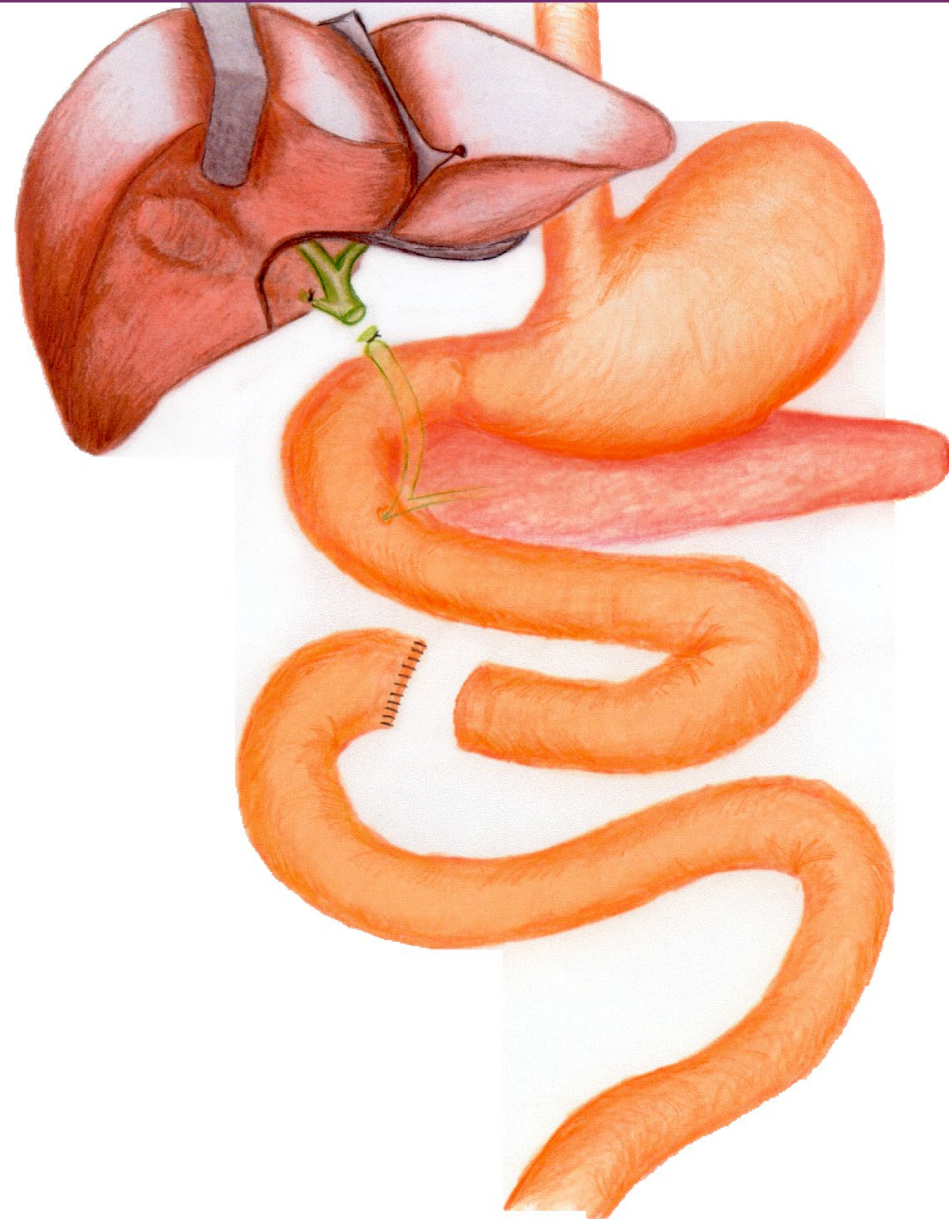
RHV to cava

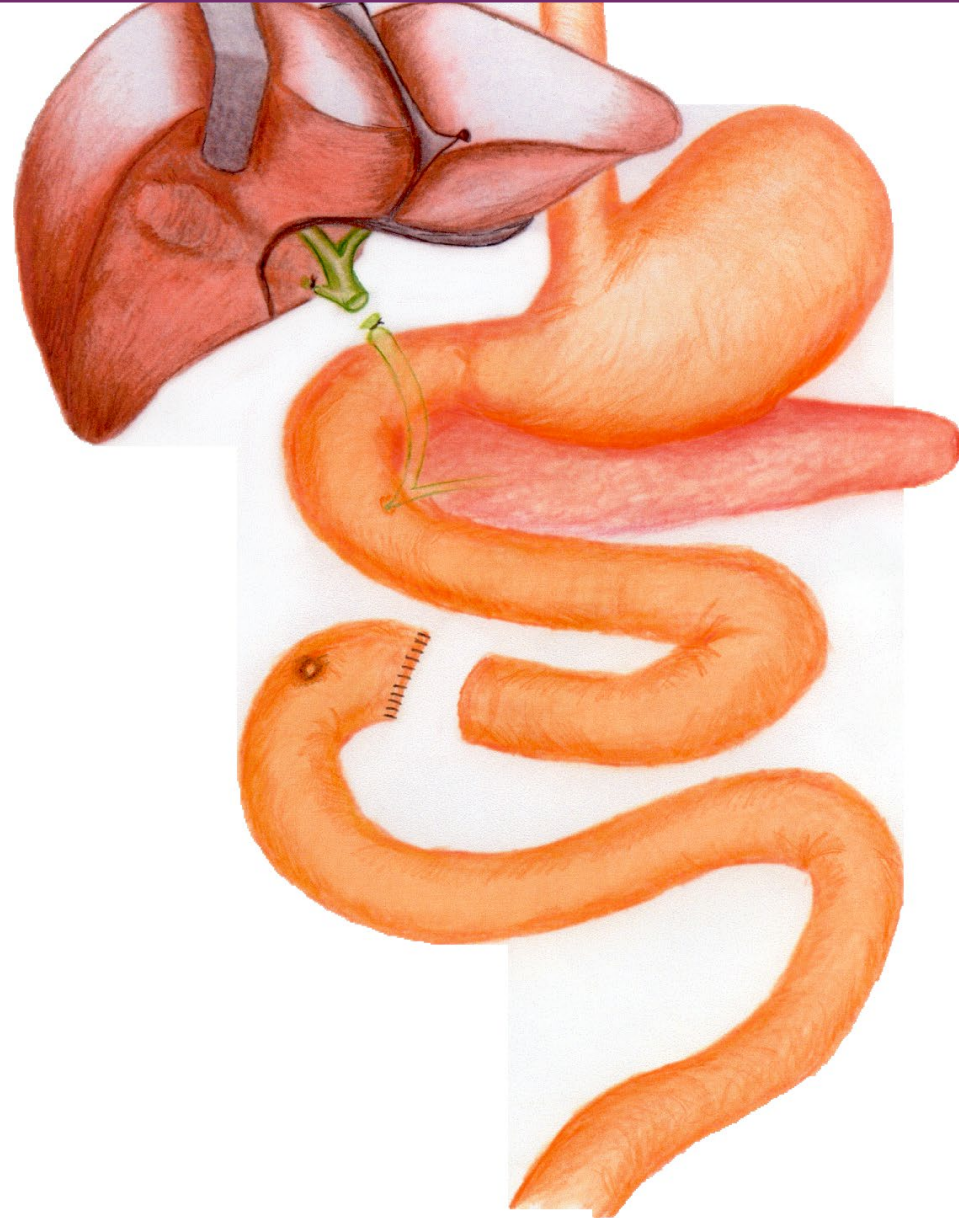
Seg 5 and two seg 8 veins to LHV

RPV to SMV jump graft

Two ducts sewn separately with ext caths

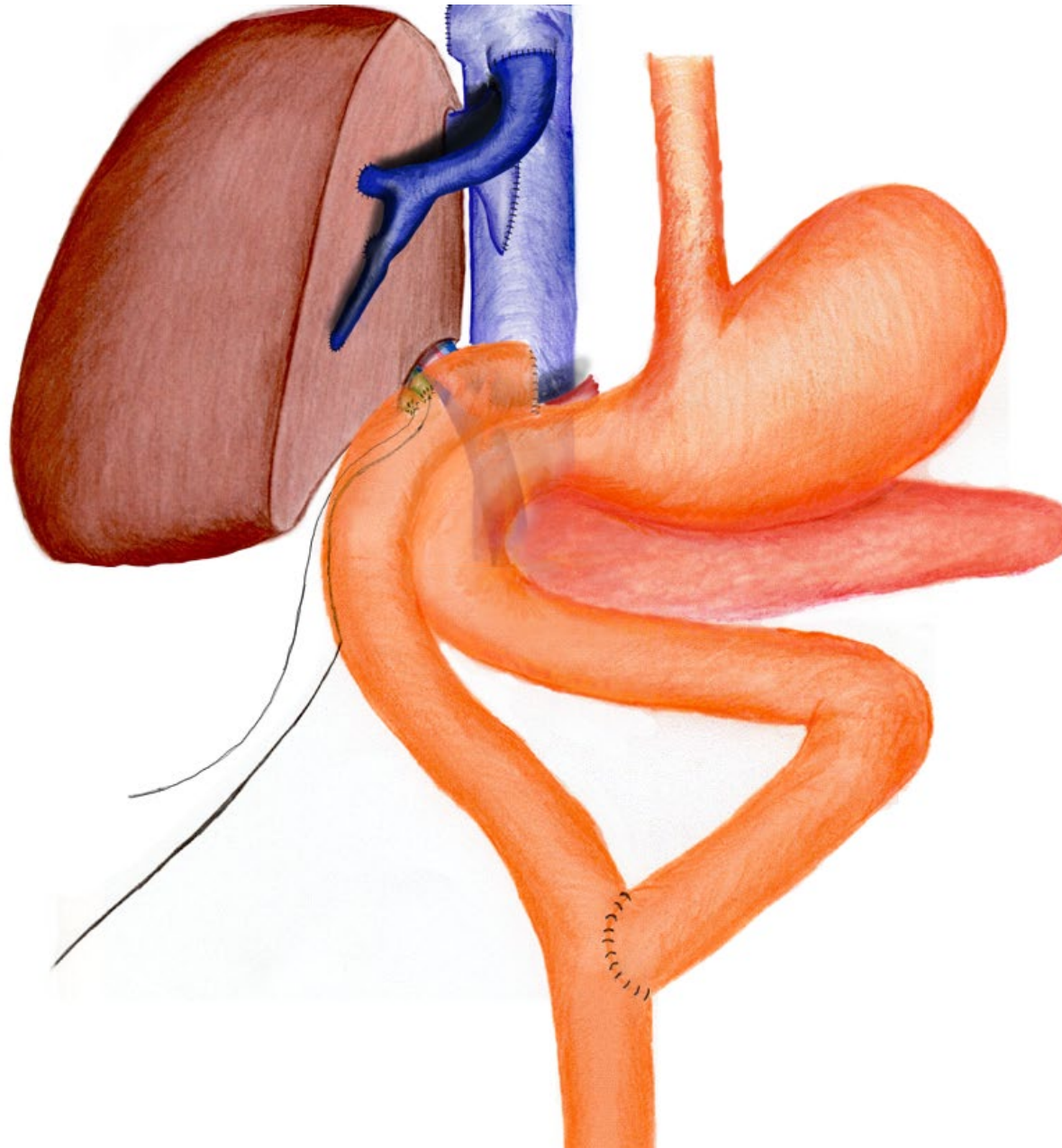












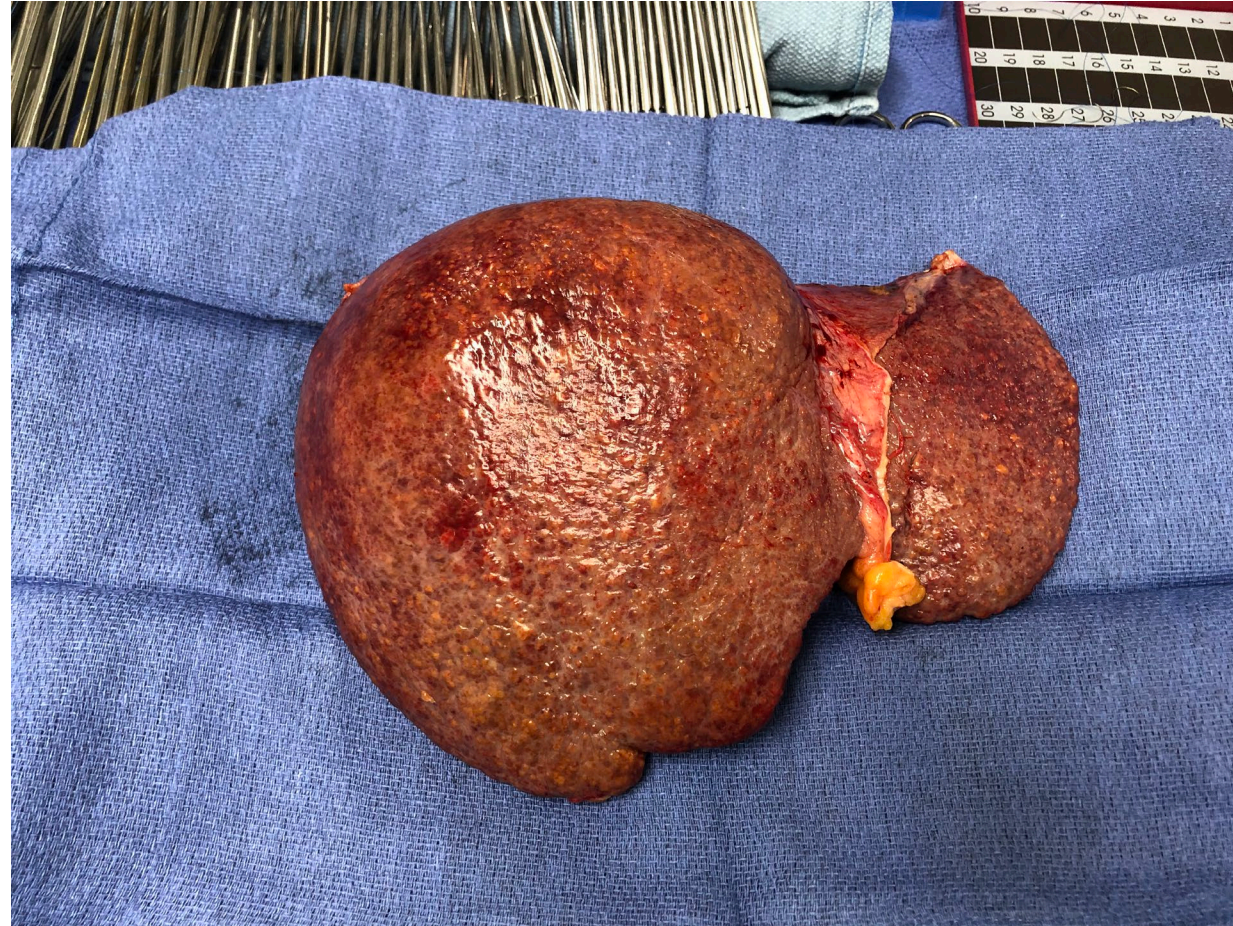
Right Lobe  
RHV to cava  
Seg 5 and two seg 8 veins to LHV  
RPV to SMV jump graft  
Two ducts sewn separately with ext caths

Operative data:

Total OR time 9.5 hours

Flow Rate: Graft weight:	980 gm
Portal vein flow:	1.64 L/min
Hepatic artery flow:	70 ml/min
Portal pressure:	7 mmHg
Jump graft flow:	0.15 L/min

PRBC 0, FFP 0, Plt 0, Cryo 0



## Explant Pathology

NATIVE LIVER (1313 GRAMS), LIVING RELATED  
LIVER TRANSPLANT:

CARCINOMA WITH MICROSCOPIC FOCI OF  
HISTOCHEMICAL AND IMMUNOPHENOTYPIC EVIDENCE  
OF **CHOLANGIOLAR** DIFFERENTIATION, SEGMENT  
5/6, **5.5 CM**

Nodes Negative.





No chemo post-op

5/13/20—no evid mets at 18 months



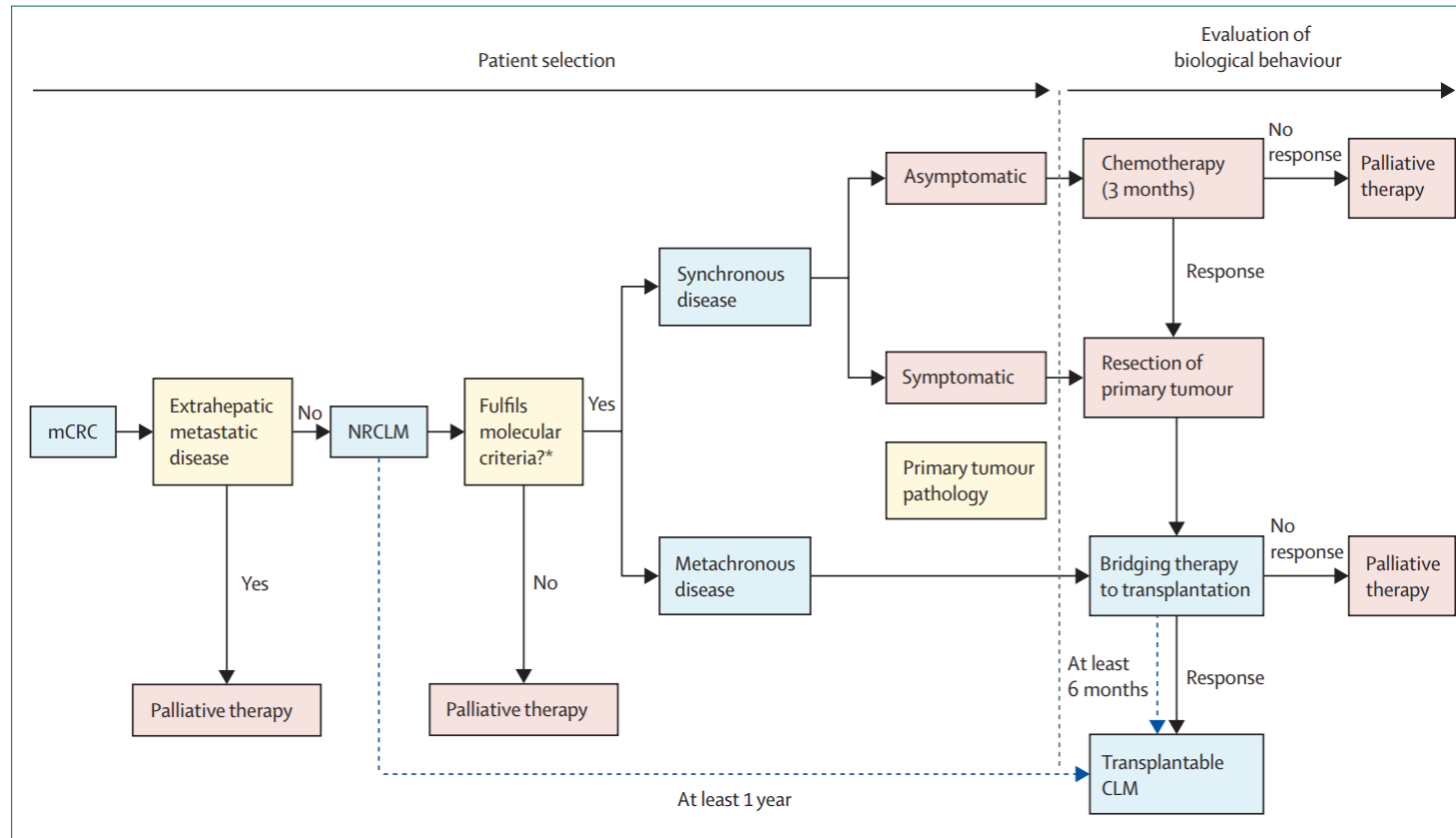
## The New Era of Transplant Oncology: Liver Transplantation for Nonresectable Colorectal Cancer Liver Metastases

Table 1

Published series on LT for NRCLM.

Study	Year	N	Overall survival			Recurrence
			1 year	3 years	5 years	
Prior to 2000						
Mühlbacher et al. [33] <sup>§</sup>	1991	25	76%	32%	12%	64%
Penn [37] <sup>*</sup>	1991	10	38% in 2-years		21%	70%
ELTR [39]	1995	58	73%	36%	18%	
After 2000						
Hagness et al. [41]	2013	21	95%	68%	60%	90%
Toso et al. [42]	2017	12	83%	62%	50%	50%

## International Consensus Group



**Figure 2: Proposed management algorithm**

CLM=colorectal liver metastases. mCRC=metastatic colorectal cancer. NRCLM=non-resectable CLM. \*No BRAF V600E mutation, microsatellite stable, and mismatch repair proficient.

66 yo male

Liver lesion biopsied showing adenocarcinoma

Rectal adenocarcinoma, 3 cm, removed

December 2016--Started FOLFOX, continued through April 2017

January 2017—Y90 to whole liver

May 2017—PET scan shows complete response (no uptake in region of rectum or liver)

August 2017—recurrent disease in right lobe of liver, restarted FOLFOX/Avastin  
FOLFOX 10 cycles through July 2018  
Avastin d/c'd May 2018 after GI bleed

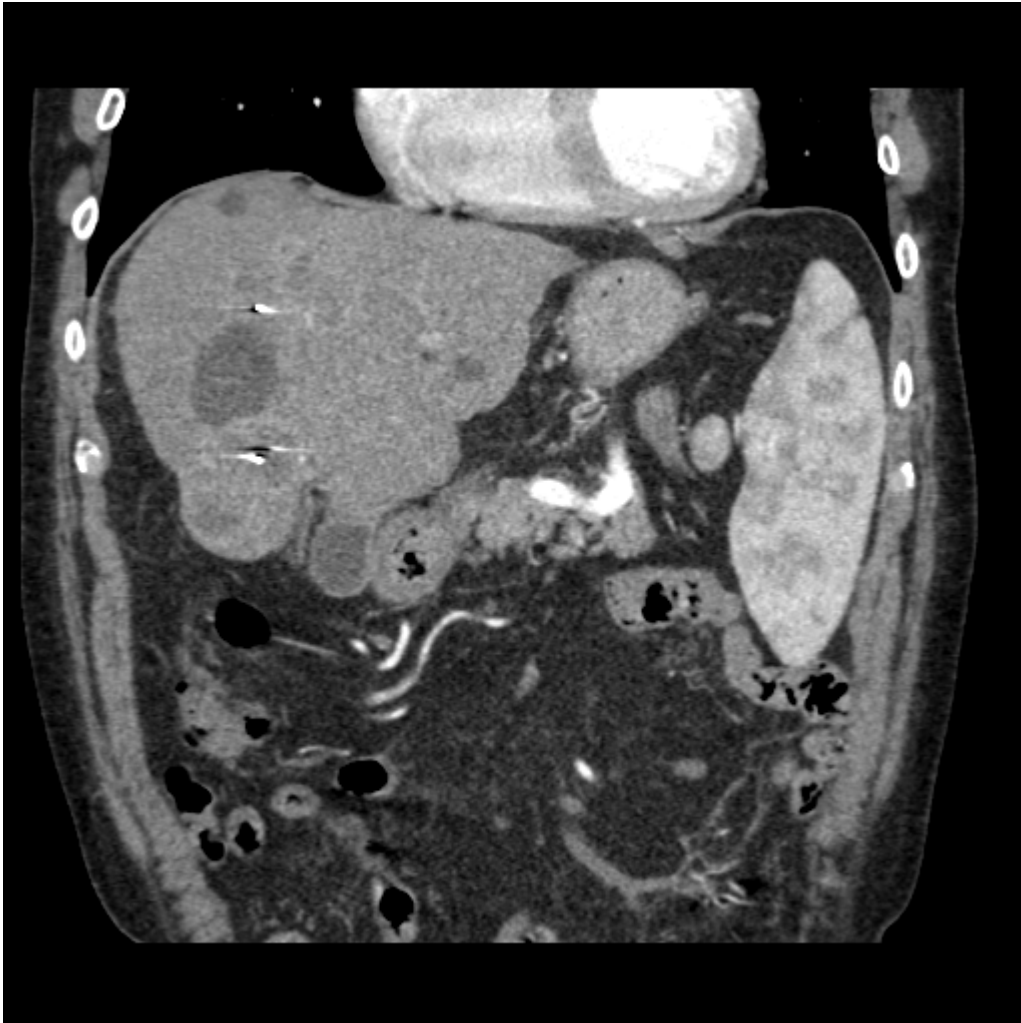
May 2018—colonoscopy negative and biopsies of previous area negative

June 2018—Near complete response via PET in liver, pelvis still negative

September 2018—recurrence right lobe, pelvis still negative  
started FOLFIRI with partial response

September 2019—Presented to UPMC for transplant evaluation

Preop CT 8/21/19



\*PET scan at OSH negative except for liver uptake

- Histologically confirmed colorectal liver metastasis non-amenable to curative hepatic resection
- LT to be considered at least 6 months after diagnosis/resection of primary tumor
- Received at least 6 to 12 weeks of chemotherapy with no evidence of disease progression
- No signs of local recurrence on colonoscopy, within the past 6 to 12 months before LT evaluation
- No signs of local or extra hepatic metastases on CT CAP /MRI/ PET CT, Bone scan at time of LT evaluation

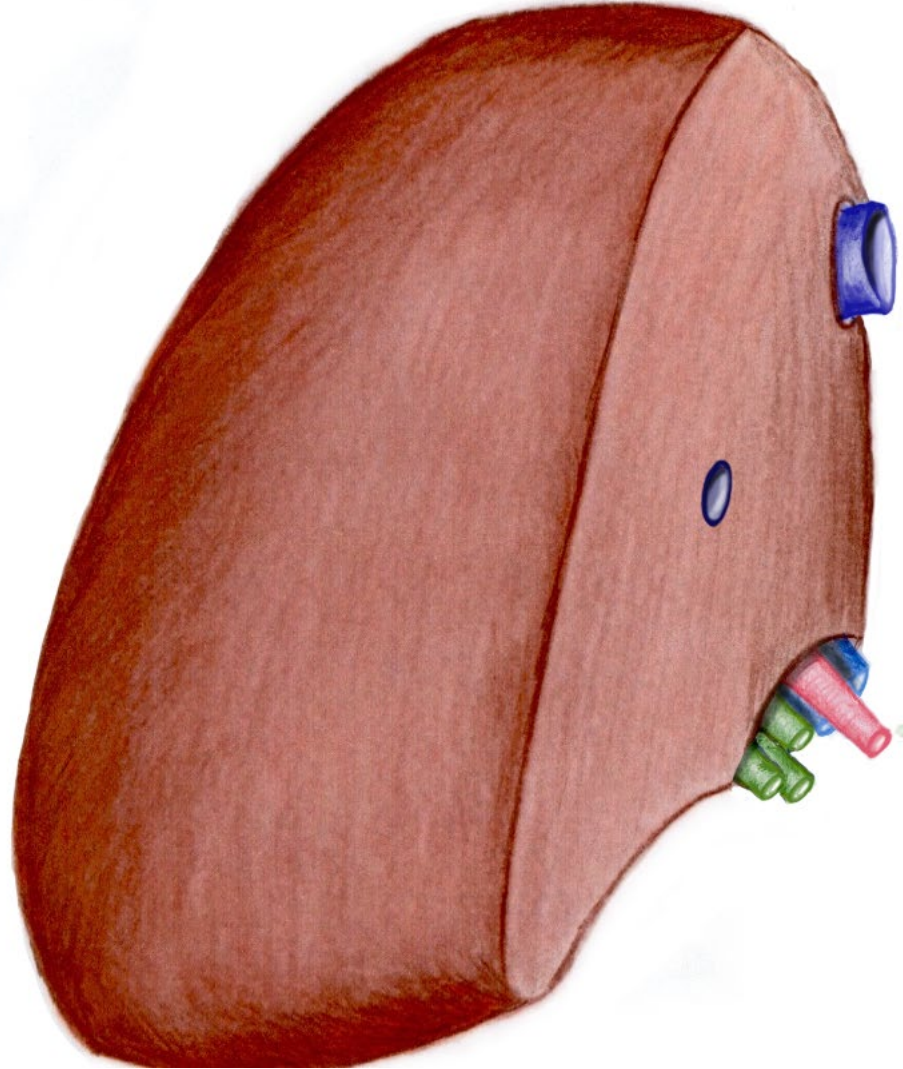
11/11/19

Ex lap, no evid extrahepatic disease

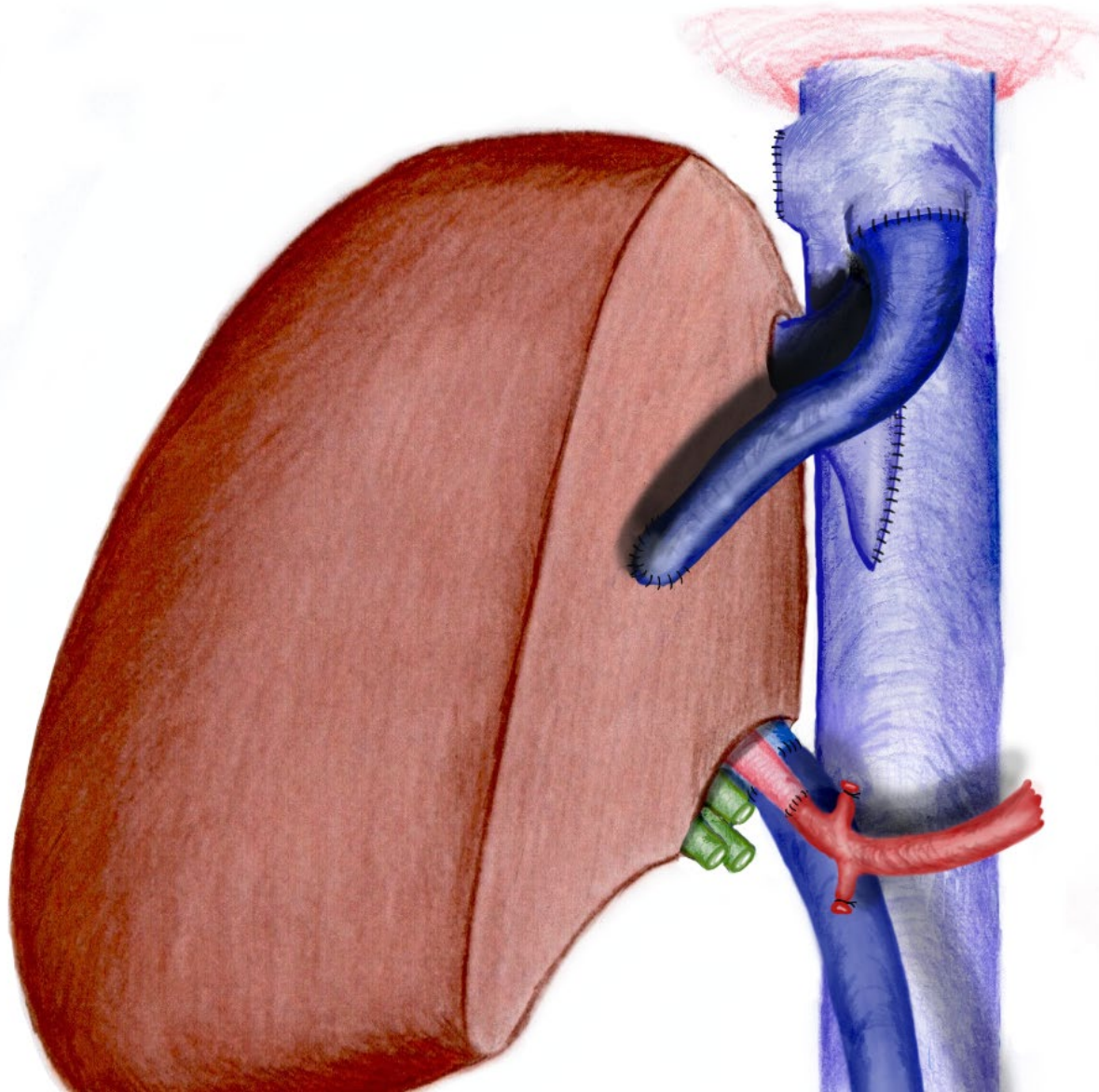
PATH:

MESENTERIC NODULE WITH FAT NECROSIS, FIBROBLASTIC PROLIFERATION AND FOCAL SCLEROTIC VENOPATHY; NO EVIDENCE OF MALIGNANCY.

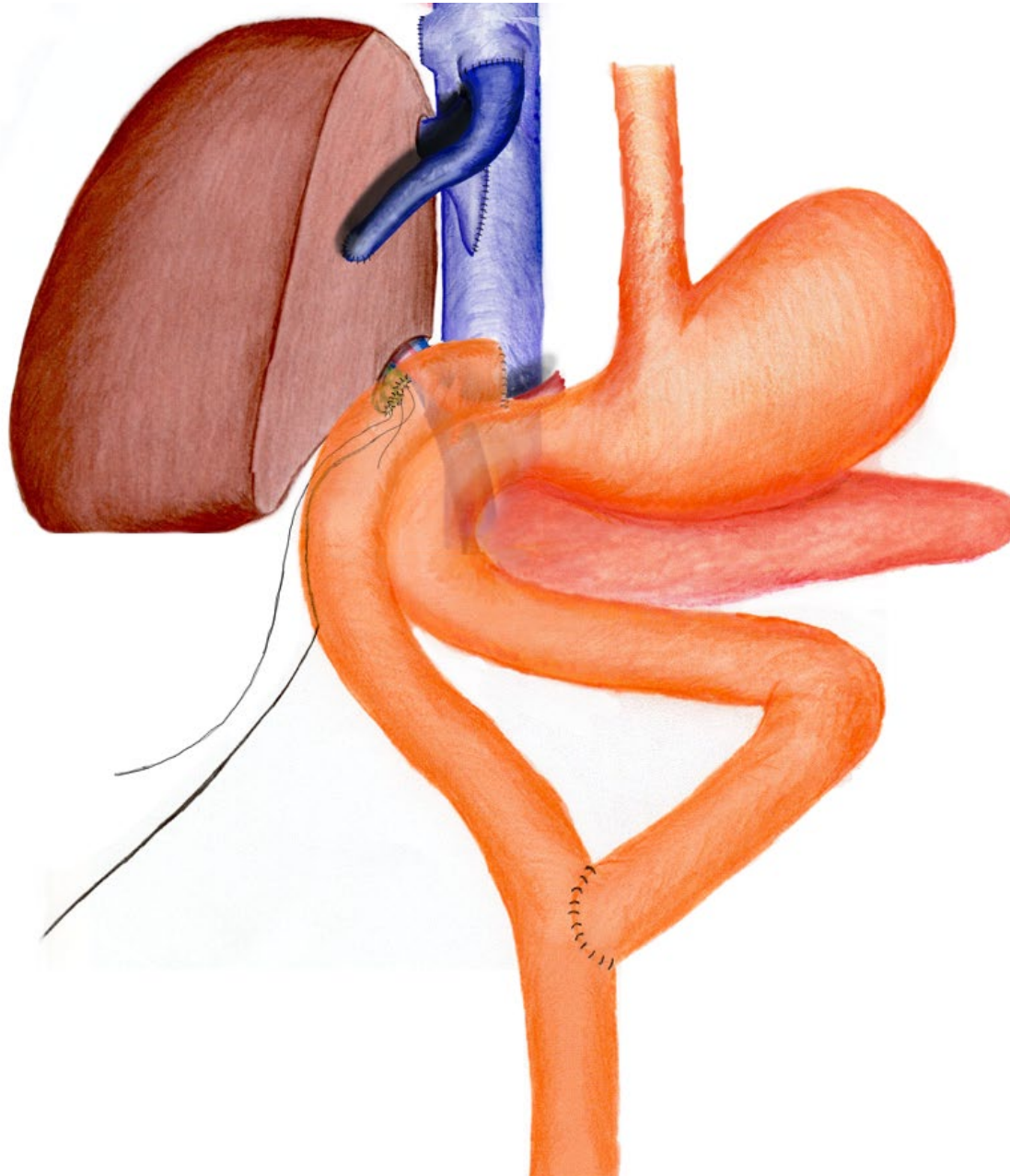




RHV to RHV  
MHV Jump to M/L HV  
RHA to RHA  
3 RHD sewn as single, 2 ext, 1 int



RHV to RHV  
MHV Jump to M/L HV  
RHA to RHA  
3 RHD sewn as single, 2 ext, 1 int



RHV to RHV  
MHV Jump to M/L HV  
RHA to RHA  
3 RHD sewn as single, 2 ext, 1 int

Total Operating time 11.1 hours

Flow Rate: Graft weight:	950 gm
Portal vein flow:	1.96 L/min
Hepatic artery flow:	62 ml/min
Portal pressure:	13 mmHg
Jump graft flow:	0.60 L/min

Packed red blood cells: 0 units, Cell saver blood: 0 cc's, Fresh frozen plasma: 0 units, Platelet packs: 0

FINAL DIAGNOSIS:

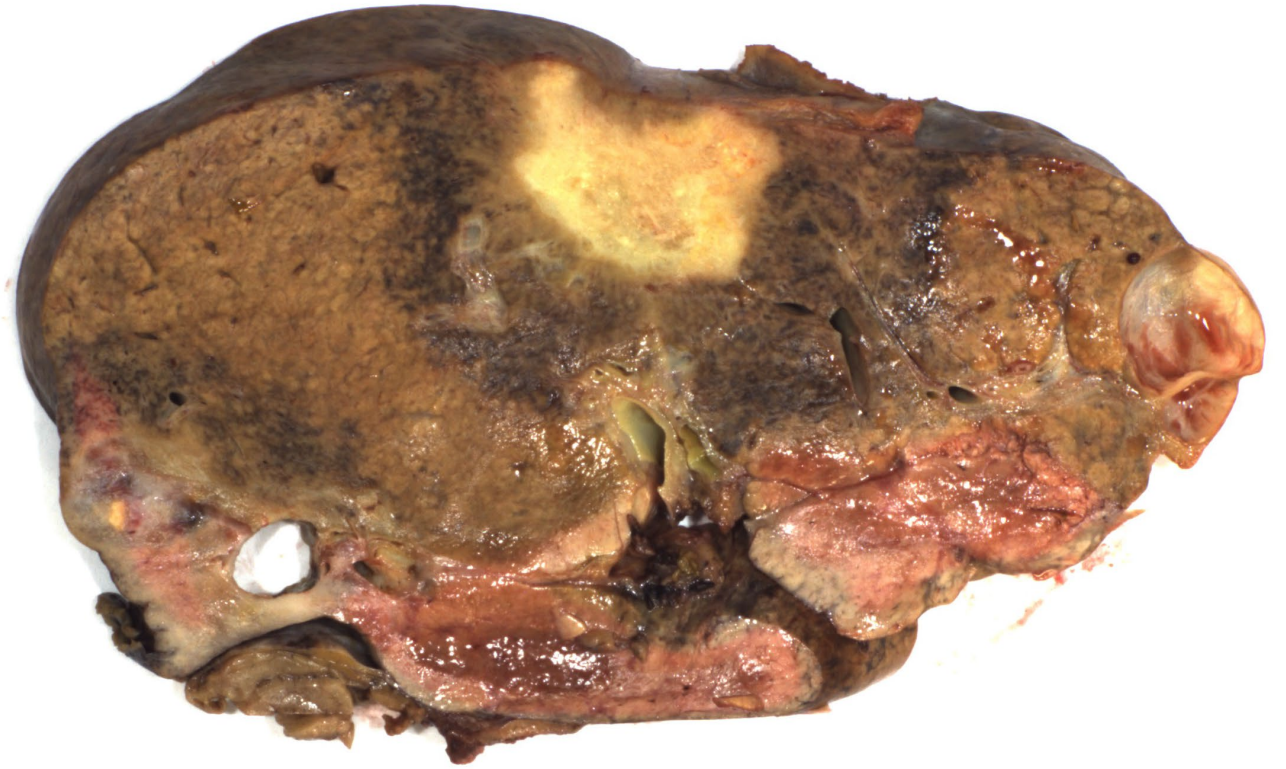
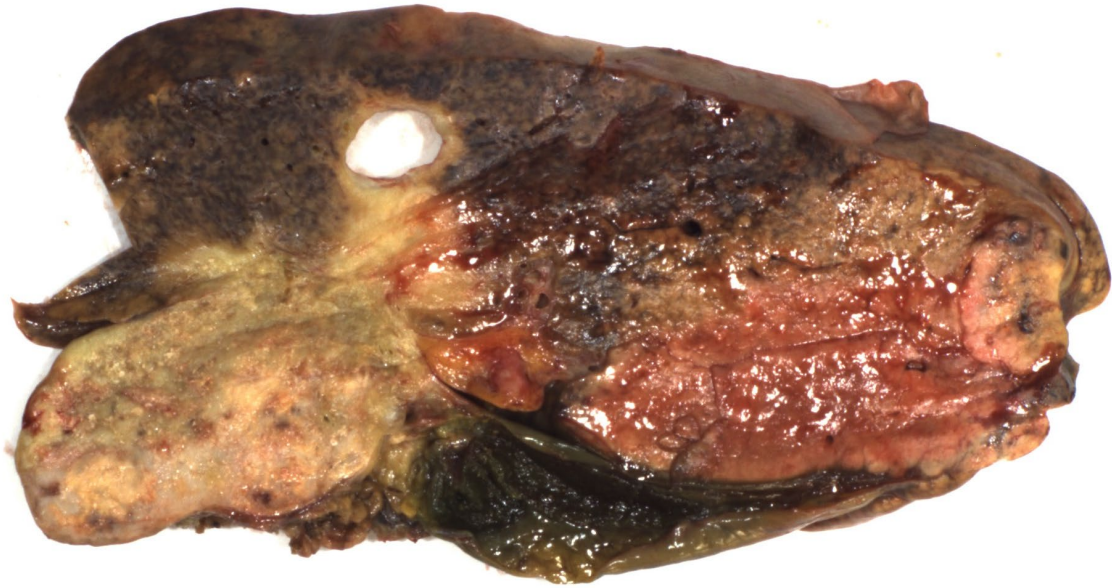
NATIVE LIVER, HEPATECTOMY (1289 GRAMS):

POORLY DIFFERENTIATED CARCINOMA: 4 SEPARATE LESIONS, PARTLY  
NECROTIC, (LARGEST 8.3 CM)

SURGICAL RESECTION MARGINS NEGATIVE FOR CARCINOMA

NO PDL-1 EXPRESSION IN TUMOR CELLS (<1% OF CELLS)

NUMEROUS INTRAVASCULAR RADIOEMBOLIC BEADS WITHIN THE TUMOR



Now 2 years post-transplant with no evidence of recurrent disease



Liver transplantation is a viable option for selected patients with:

- Hilar or Intrahepatic Cholangiocarcinoma
- Isolated Colorectal Metastasis
- LDLT provides advantages for these patients to reduce number of surgeries and waiting time for transplant