



Case Presentation

Janeen Jordan, MD

Surgical Grand Rounds

December 21, 2009



YG 61yo Russian Male

- 10/2009 Presented to OSH with painless jaundice and 25 pound weight loss over 1month
- Labs showed T. Bili 8.4
- Work up included:
 - US: dilated bile duct 14mm, no panc mass
 - CTAP: dilation of pancreatic duct without mass
 - ERCP: stricture of mid/distal bile duct; brushings negative for malignancy
 - ERCP: repeat secondary to stent occlusion; brushings still negative
- Sent to UCH for second opinion



YG 61yo Russian Male

- PMHx: CAD s/p drug eluting stents x3, HTN, DM
- PSHx: none
- Meds: Metoprolol 25mg Bid, Lisinopril 10mg daily, Januvia 100mg daily
- Allgy: NKDA
- SocHx: no t/e/i. Immigrated from Russia 15yrs ago with his wife. Works as a salesman
- FMHx: Mother with DM, HTN; Father with prostate cancer

YG 61yo Russian Male

- Seen by Dr. Shah, Gastroenterology
- Increased abdominal pain

$\frac{133}{3.1} \mid \frac{89}{33} \mid \frac{18}{1.02} \leftarrow 133$

$7.4 \swarrow \frac{10.3}{31.4} \searrow 205$

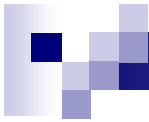
Lipase 20

$\frac{6.8}{105} \mid \frac{3.7}{166}$
 $\frac{2.0}{169} \mid \frac{1.2}{169}$

- EUS 11/18/2009

- ☐ Suspicious 12x12mm mass at mid-CBD with stricture
- ☐ Abnl lymph nodes periduodenal (4x7mm)
- ☐ FNA: rare epithelial cells, atypia c/w inflammation from stent

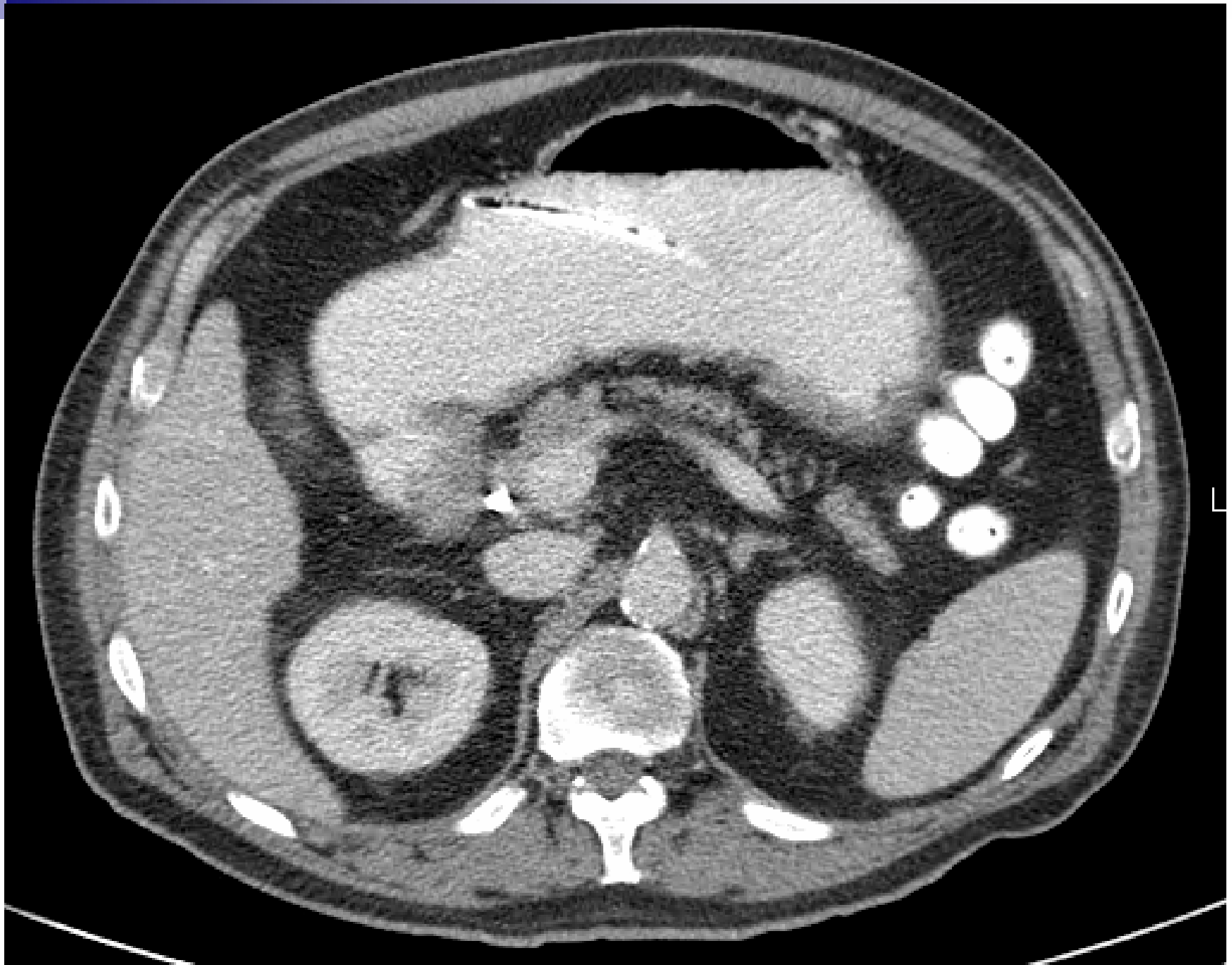
- ERCP

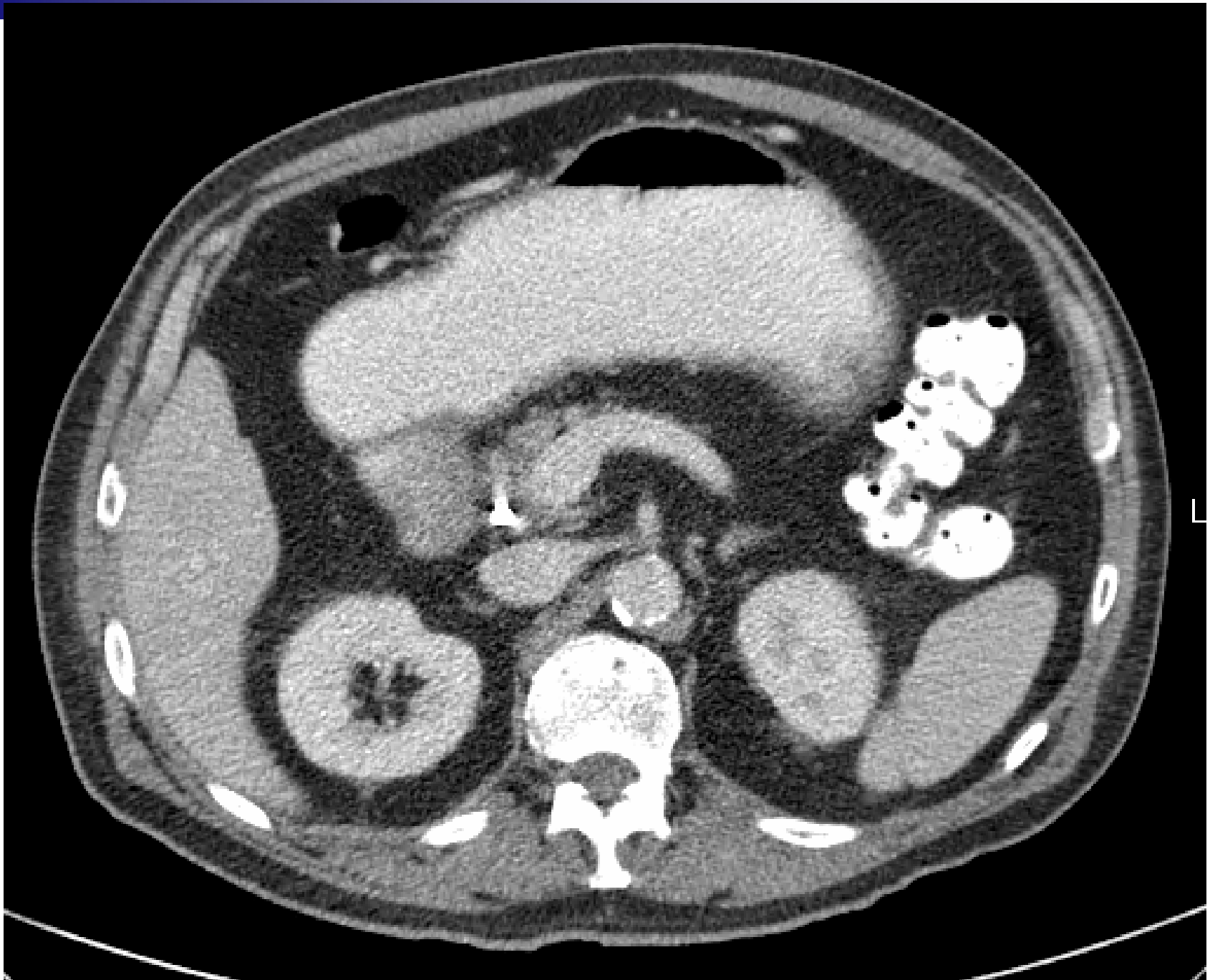


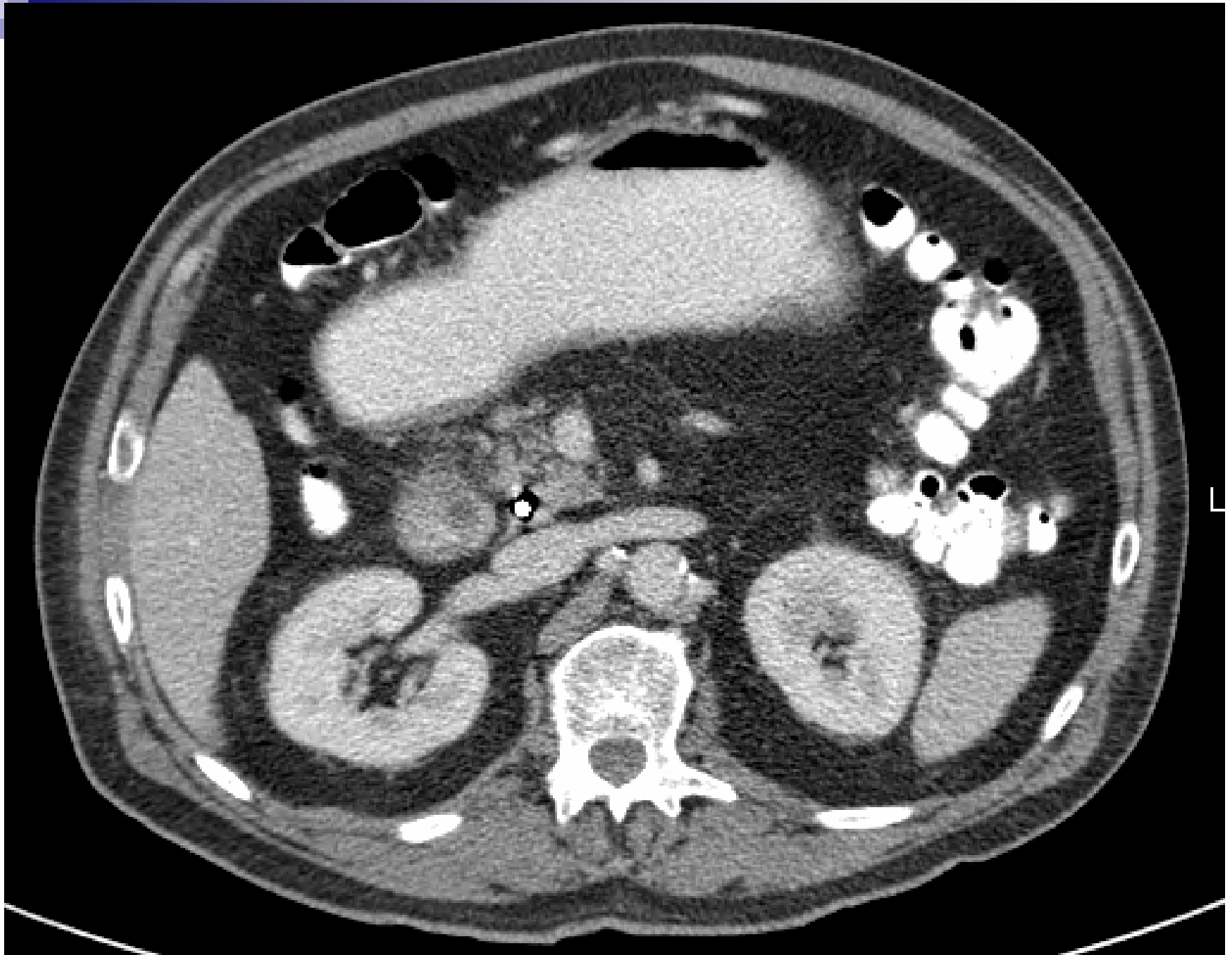


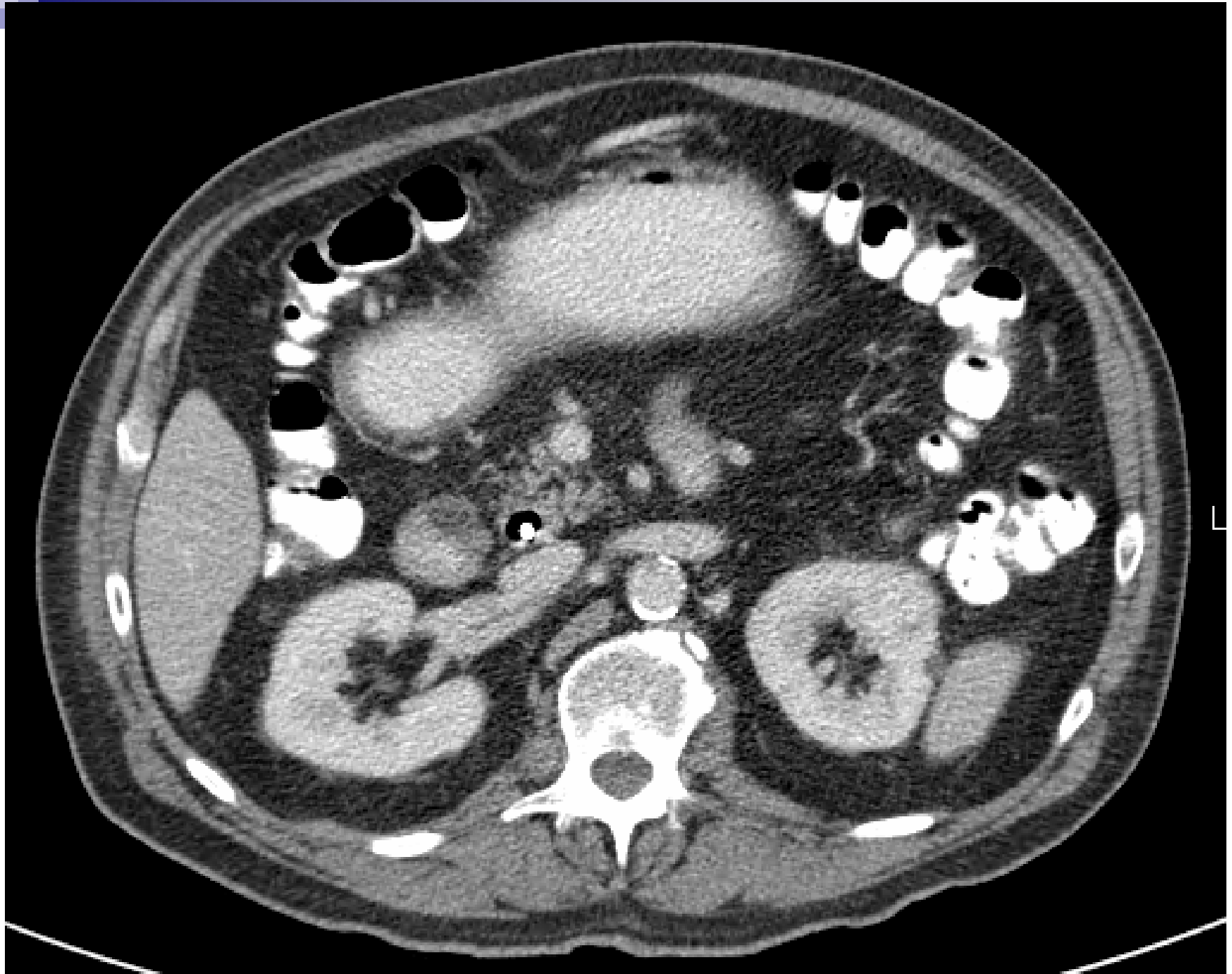
YG 61yo Russian Male

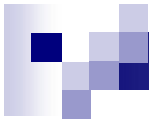
- Presents to ER 11/19/2009 with bilious emesis and po intolerance
- EGD
 - ☐ Severe esophagitis
 - ☐ Gastric outlet obstruction
 - ☐ Extrinsic duodenal mass
- Tx with NGT and ivf
- Surgical consult 11/20/2009
 - ☐ Repeat CTAP
 - ☐ CA 19-9 1813.4
 - ☐ CEA 3.9











Summary

- 61yo M Russian, non-smoker
- Painless jaundice, 25 lb weight loss
- Biliary stricture, gastric outlet obstruction
- High CA 19-9, mildly elevated CEA



Differential Diagnosis

■ Cholangiocarcinoma

- Benign Biliary Stricture
- Duodenal adenocarcinoma
- Pancreatic mass/neoplasm
- Gallbladder mass/cancer
- Duodenal diverticulum



YG 61yo Russian Male

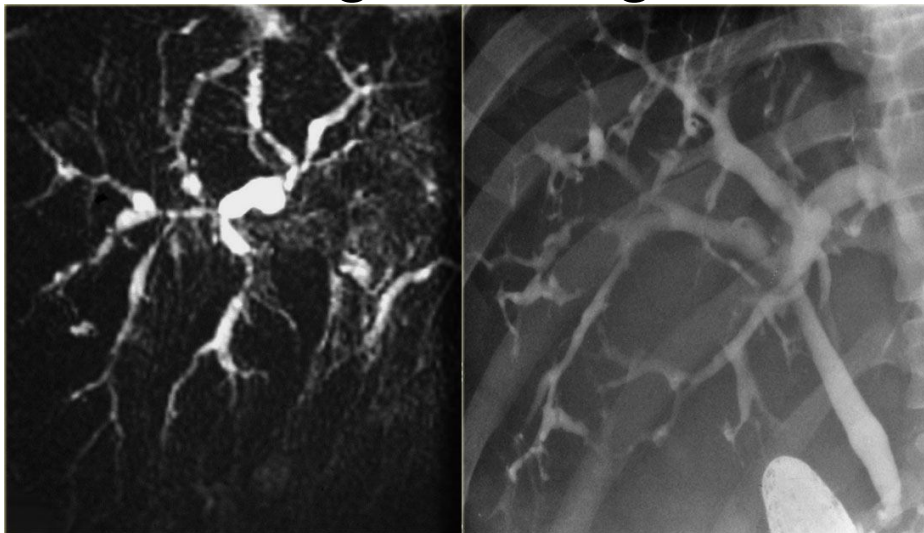
■ OR

- Exploratory laparotomy
- Abdominal exploration: 2 liver nodules, largest 1cm – shave biopsy for frozen section
 - Adenocarcinoma
- Biliary and gastric bypass
 - Loop gastro-jejunostomy
 - Roux-en-Y choledocojejunostomy
 - Gastrostomy and Jejunostomy tubes

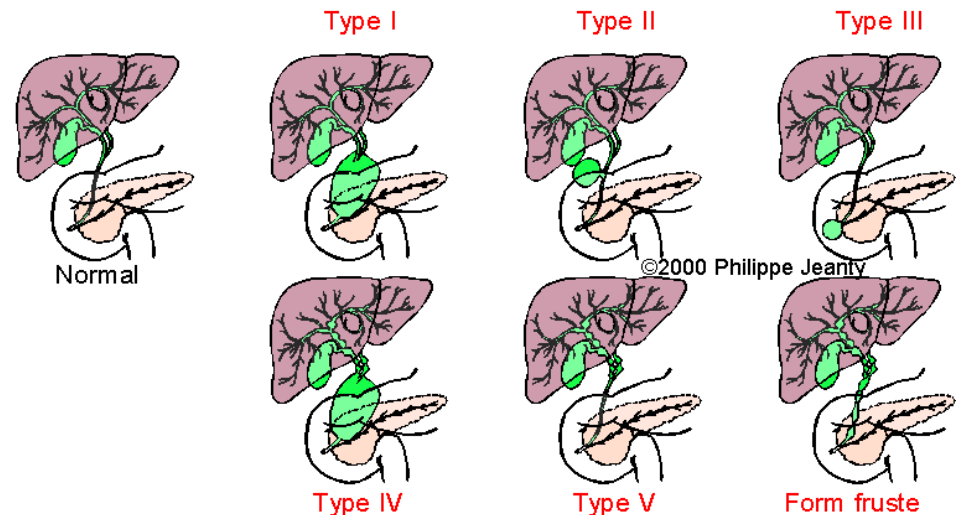
Cholangiocarcinoma

- 3% of all new malignancies
- 5000 new cases per year in US
- Asian and male preponderance
- Risk factors:

Sclerosing cholangitis (8-20%)



Choledochal cyst (3-28%)



Cholangiocarcinoma

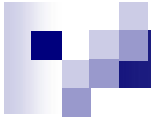
■ Presentation

Signs and Symptoms of Cholangiocarcinoma

	Intrahepatic	Perihilar	Distal
■ Abdominal pain	XX*	X	X
■ Anorexia	X	X	X
■ Weight loss	X	XX	XX
■ Pruritis	X	X	X
■ Jaundice	—	XXX	XXX
■ Distended palpable GB—		—	X
■ Abnormal AP/GGT	X	X	X

■ *From Nakeeb A, Pitt HA, Sohn TA, and others: Ann Surg 224:463, 1996.*

■ Elevated CEA or CA 19-9

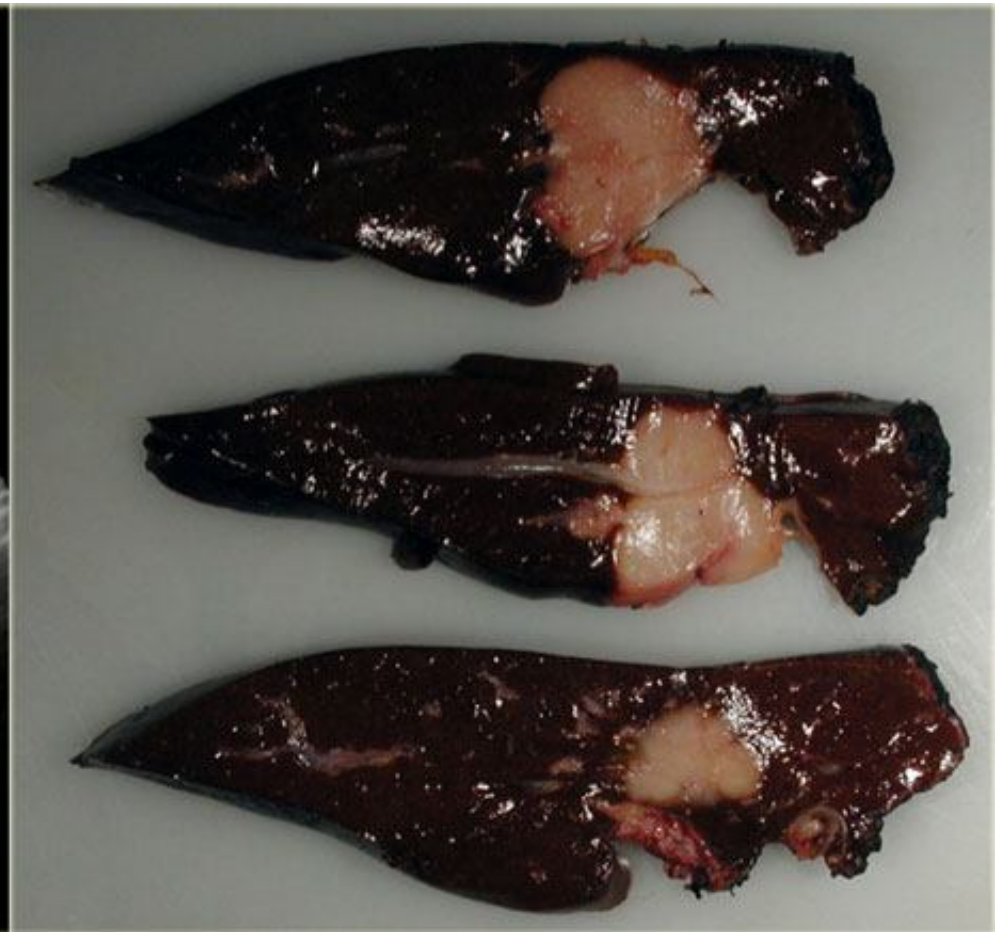
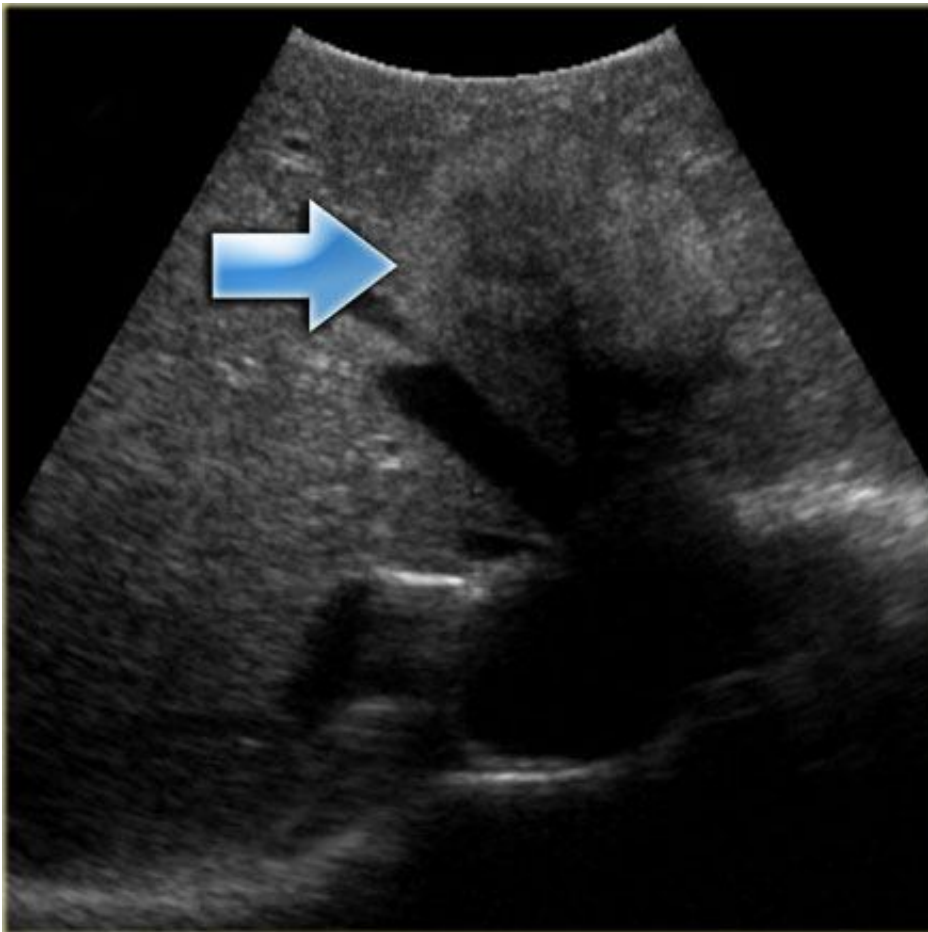


Cholangiocarcinoma

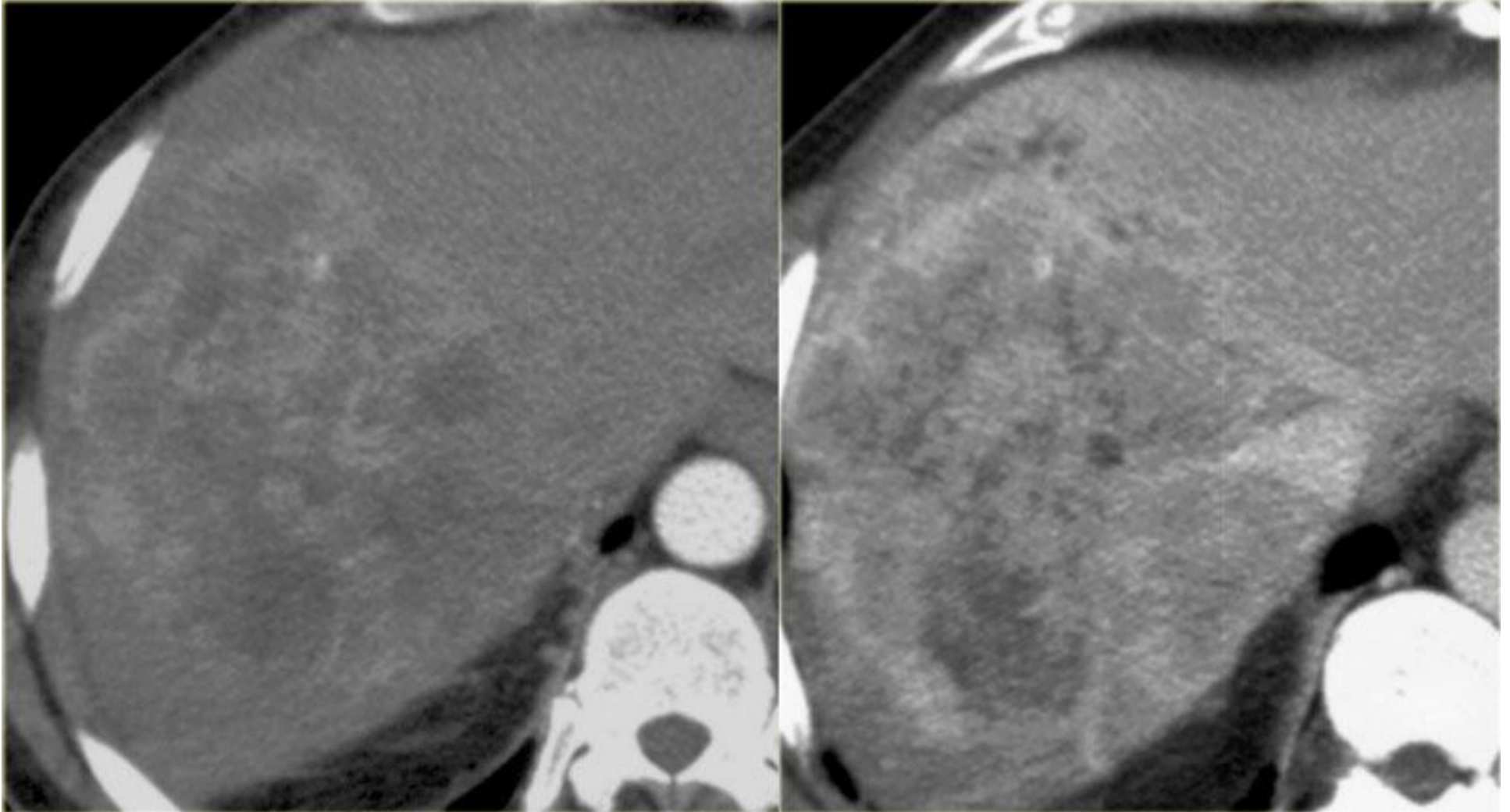
■ Imaging

- ☐ US
- ☐ CTAP
- ☐ ERCP
- ☐ PTC
- ☐ MRCP

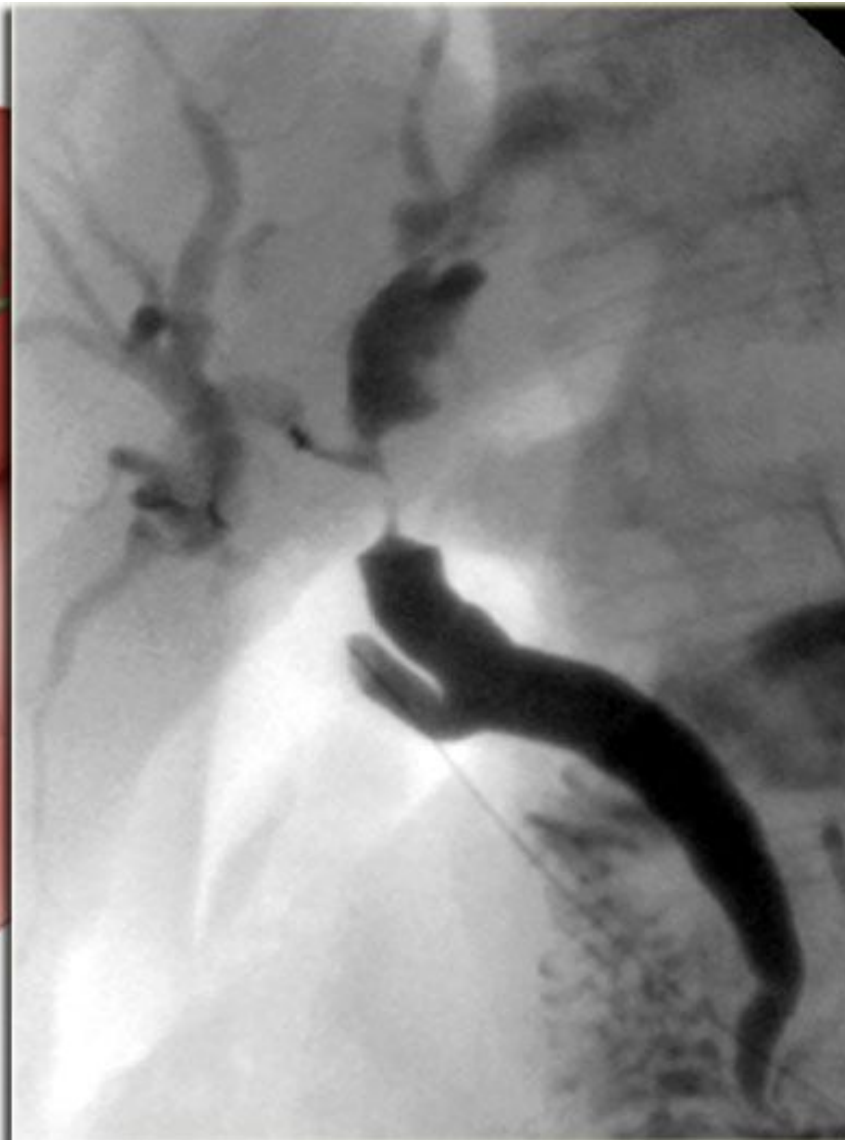
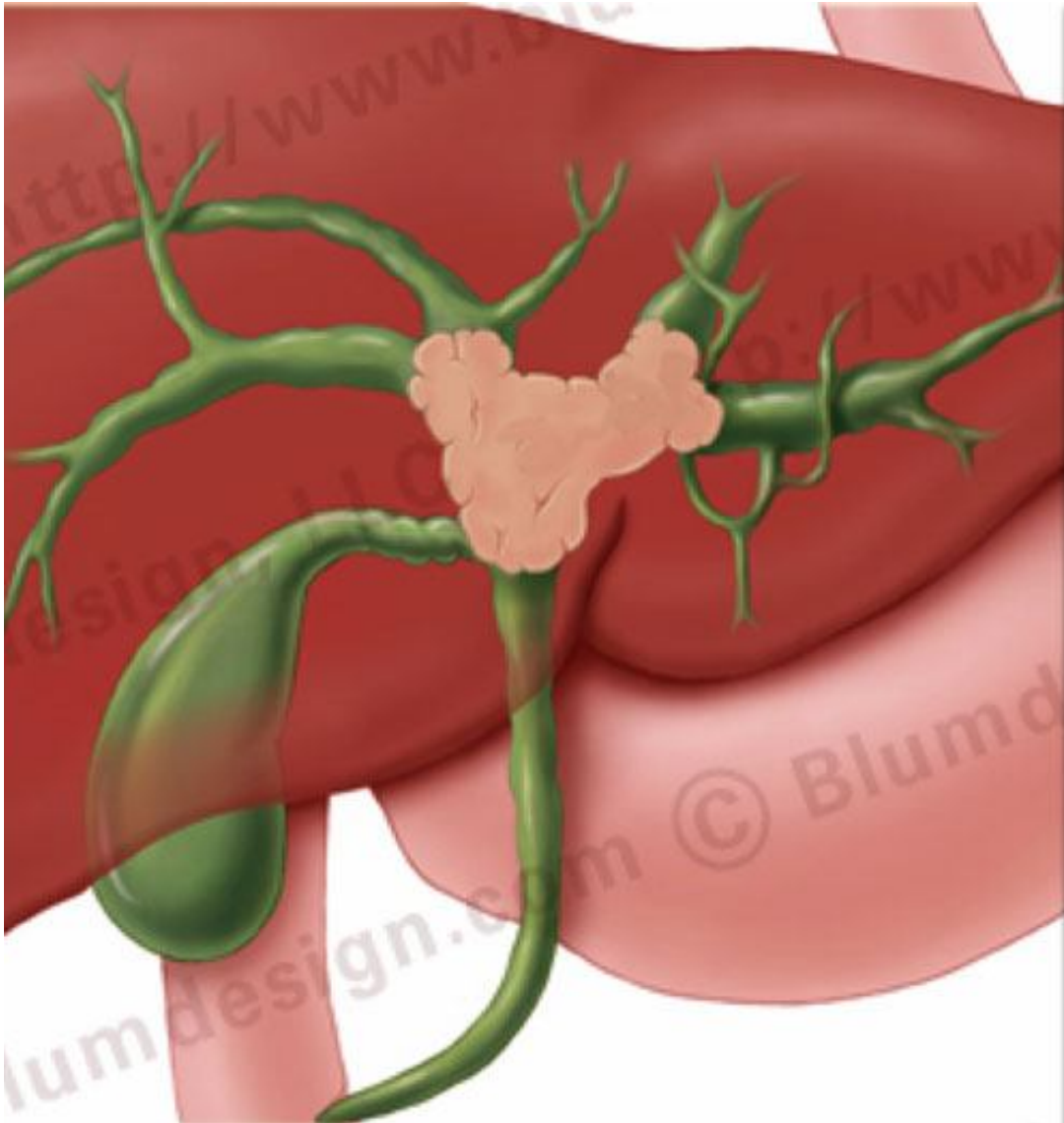
Imaging: Ultrasound



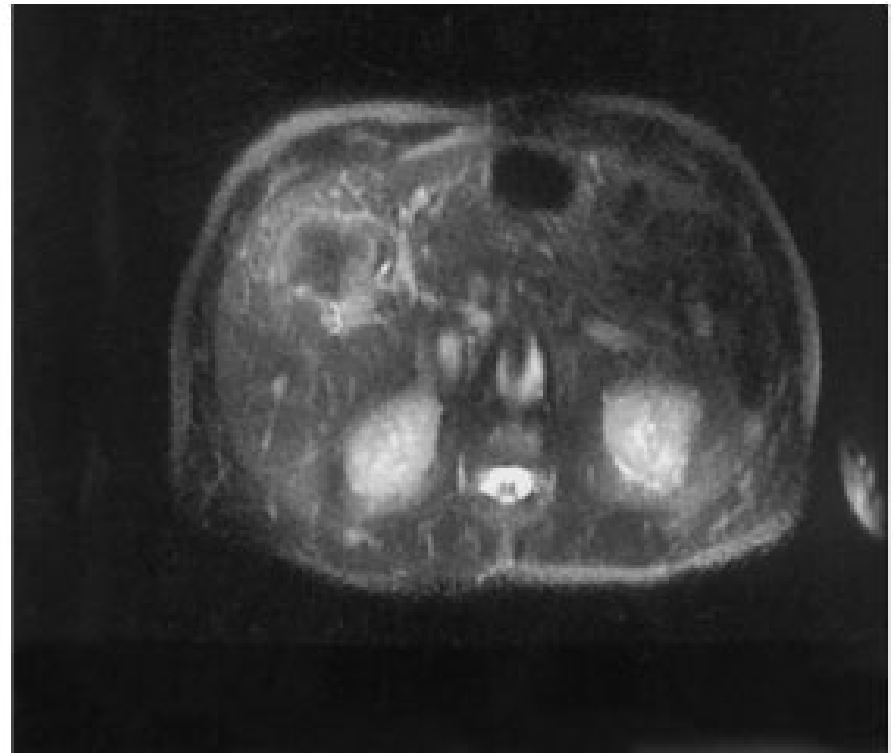
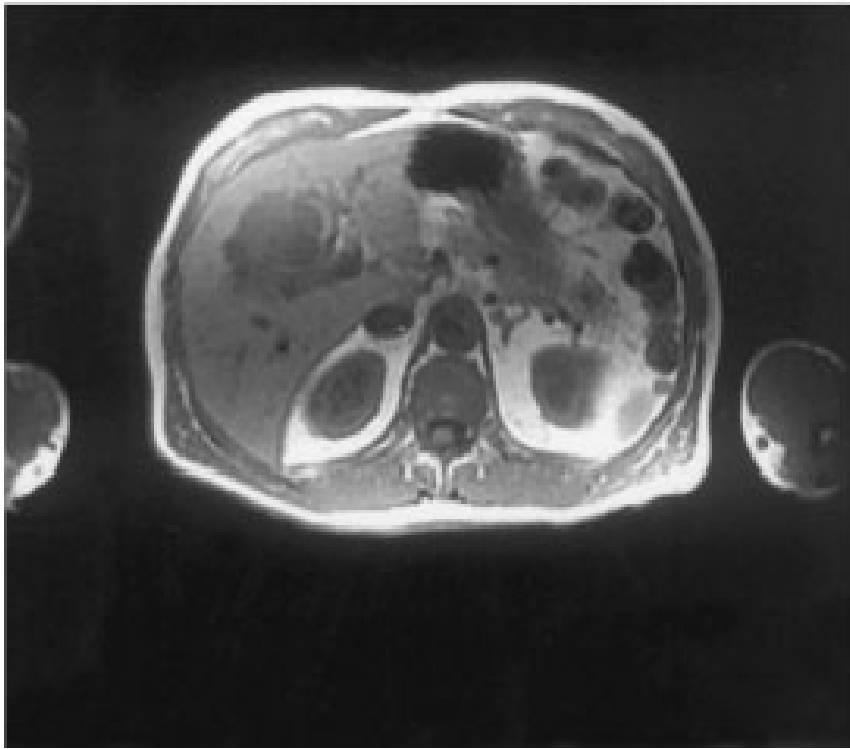
Imaging: Cat Scan



Imaging: ERCP



Imaging: MRCP



A

B



Cholangiocarcinoma

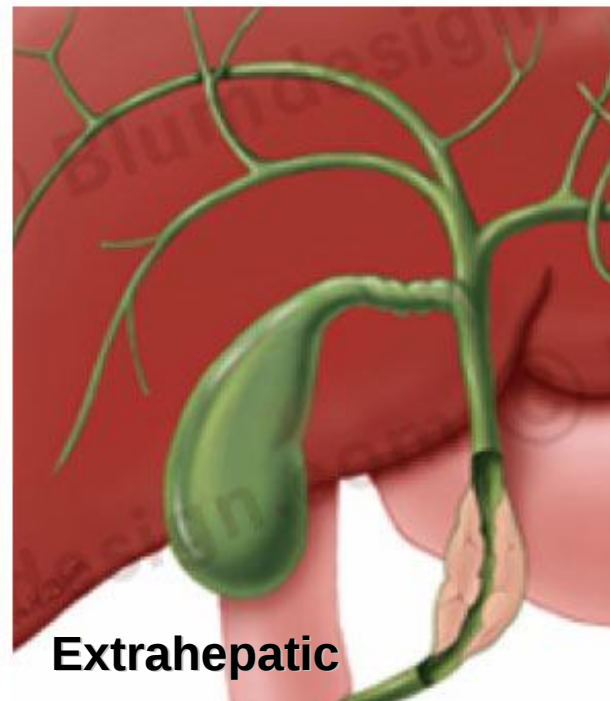
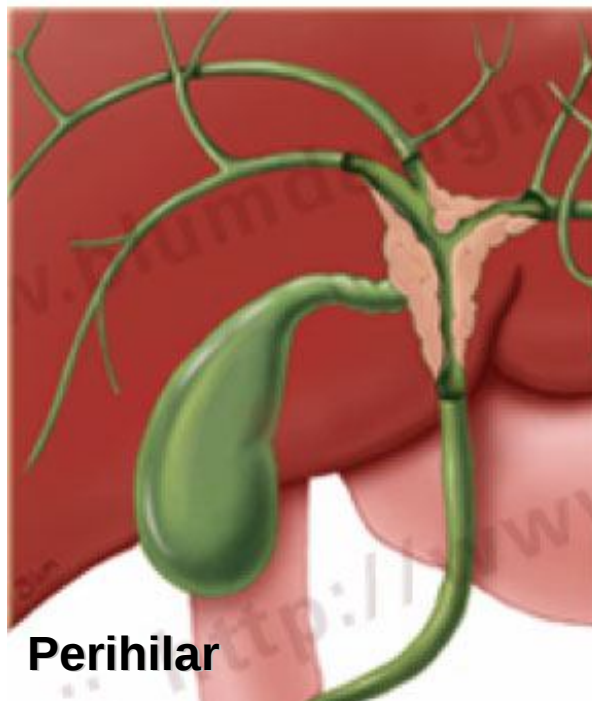
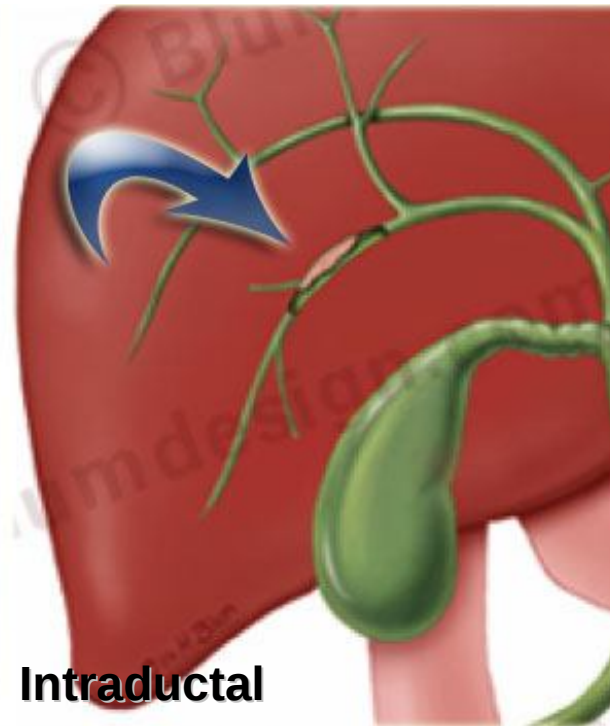
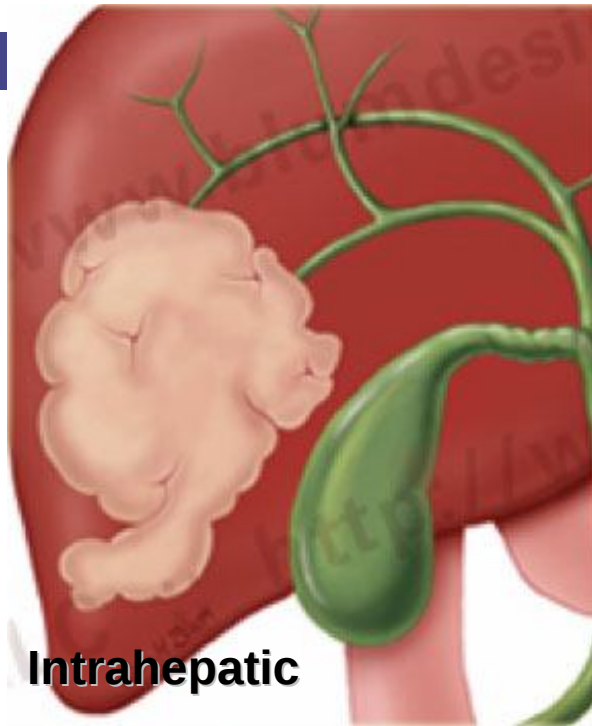
■ Pathology

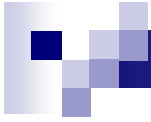
□ Macroscopic

- Intrahepatic: mass-forming, peri-ductal, intraductal
- Extrahepatic: sclerosing, nodular, papillary

□ Microscopic

- Tubular adenocarcinoma
- Papillary adenocarcinoma
- Signet-cell carcinoma
- Mucoepidermoid carcinoma
- other





Cholangiocarcinoma

- Staging
 - ☐ Bile duct involvement
 - ☐ Portal vein involvement
 - ☐ Hepatic lobar atrophy

Staging of Cholangiocarcinoma

Staging System	Stage	Tumor	Node	Metastasis
AJCC TNM intrahepatic	I	T1	N0	M0
	II	T2	N0	M0
	IIIA	T3	N0	M0
	IIIB	T4	N0	M0
	IIIC	Any T	N1	M0
	IV	Any T	Any N	M1

T1, solitary tumor without vascular invasion; T2, solitary tumor with vascular invasion or multiple <5 cm; T3, multiple >5 cm or major vascular involvement; T4, direct invasion of adjacent organ (not gallbladder) or perforation of visceral peritoneum; N1, regional LN metastases; M1, distant metastases.

AJCC TNM extrahepatic	0	Tis	N0	M0
	IA	T1	N0	M0
	IB	T2	N0	M0
	IIA	T3	N0	M0
	IIB	T1 to T3	N1	M0
	III	T4	Any N	M0
	IV	Any T	Any N	M1

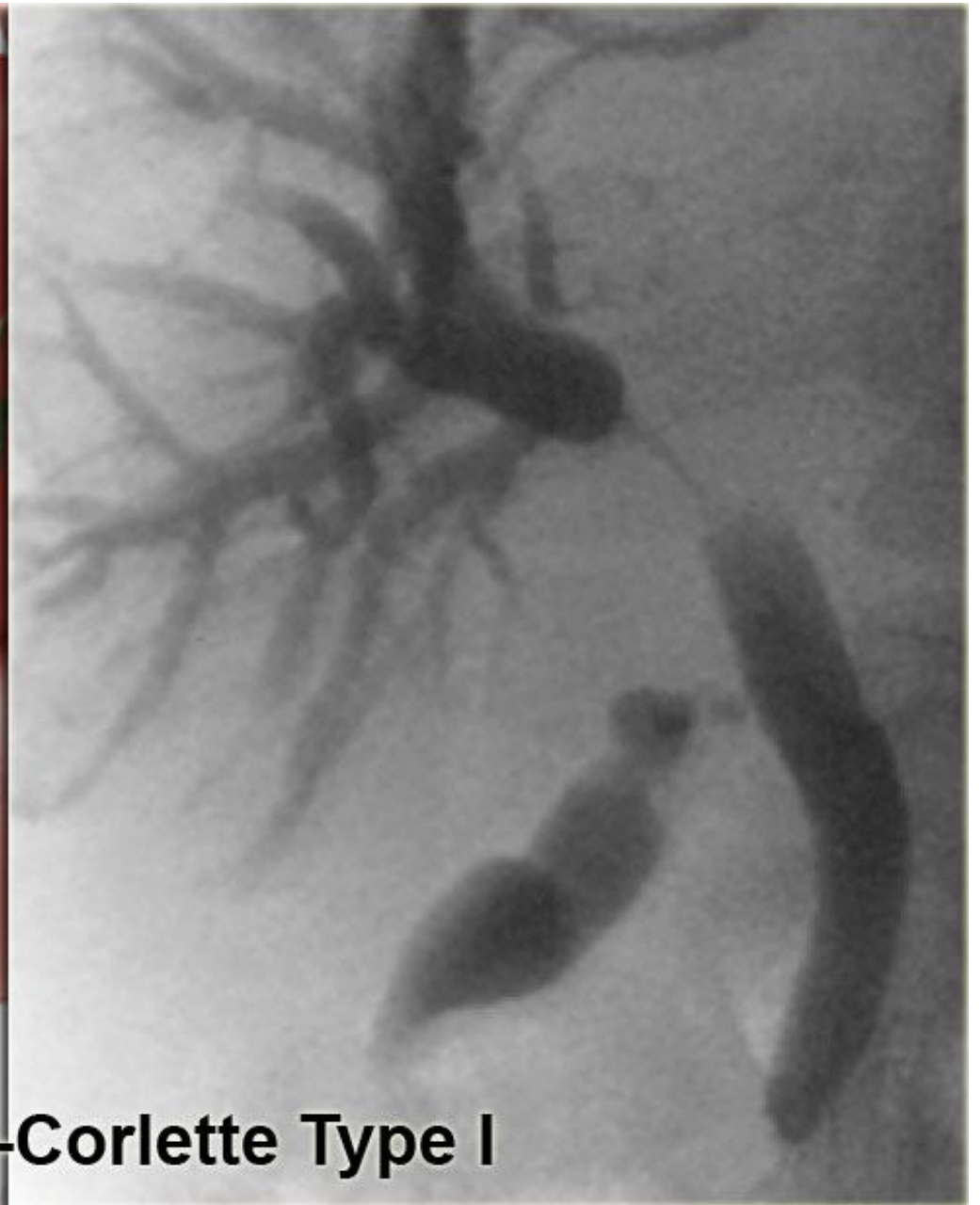
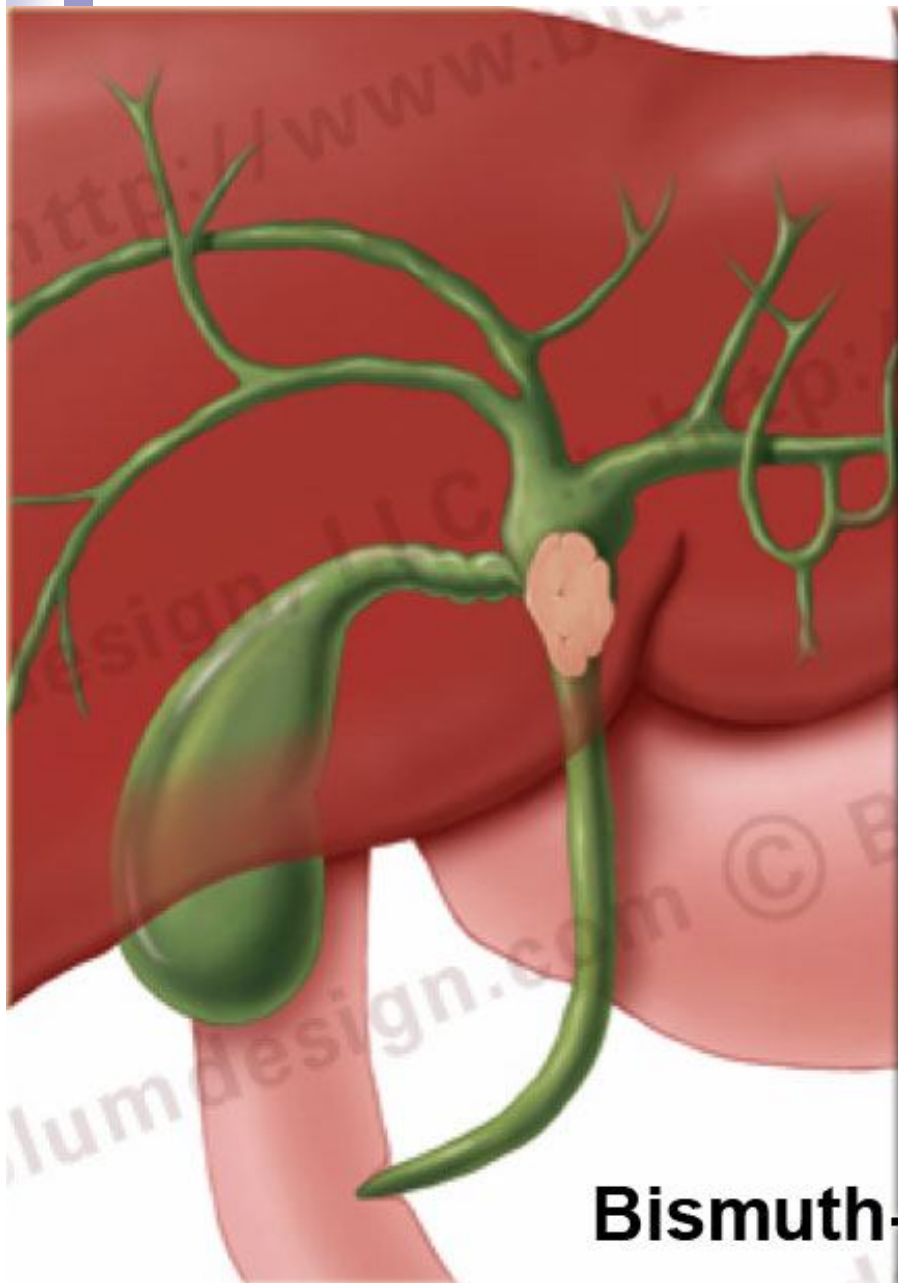
Tis, carcinoma in situ; T1, confined to bile duct; T2, beyond bile duct; T3, invades liver, gallbladder, pancreas, or unilateral HA or PV; T4, invades other adjacent organs or main HA or PV; N1, regional LN metastasis; M1, distant metastasis

Blumgart T-stage criteria perihilar Criteria

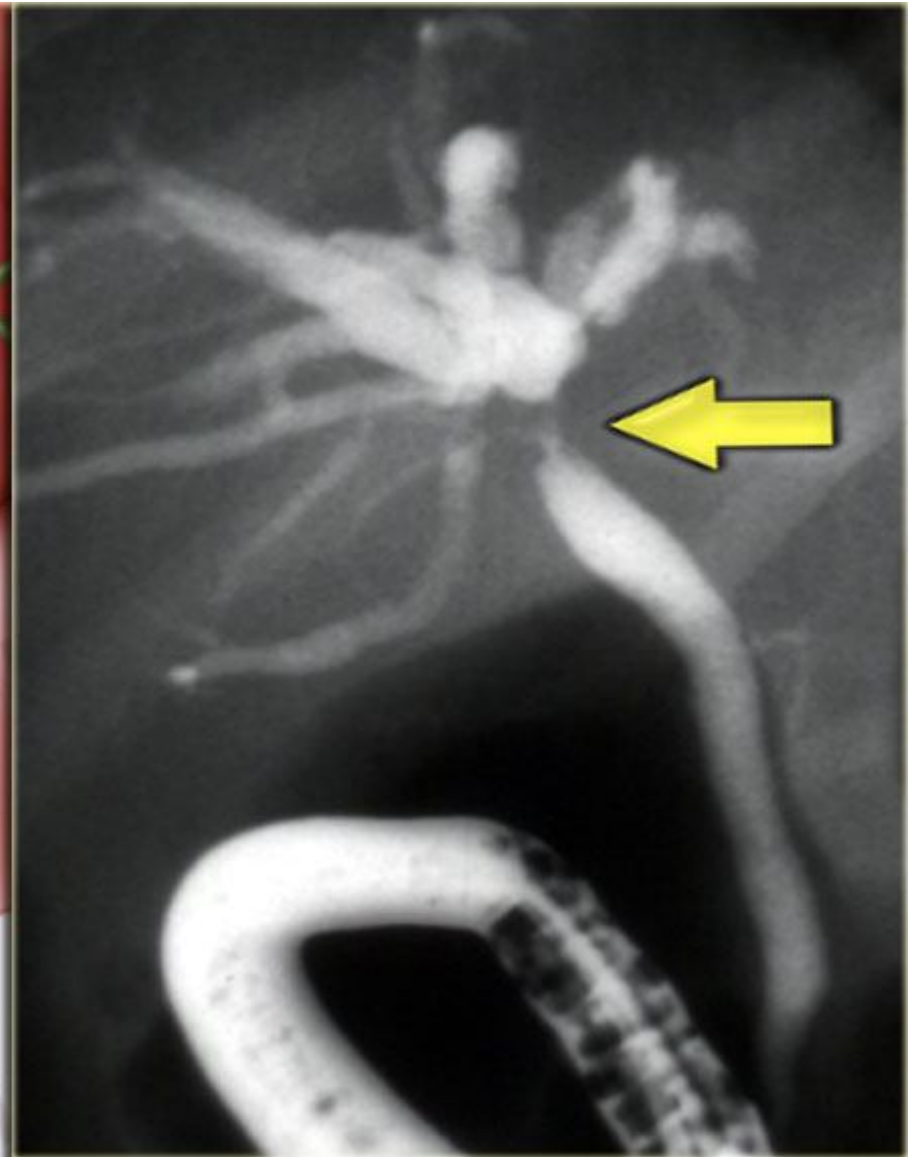
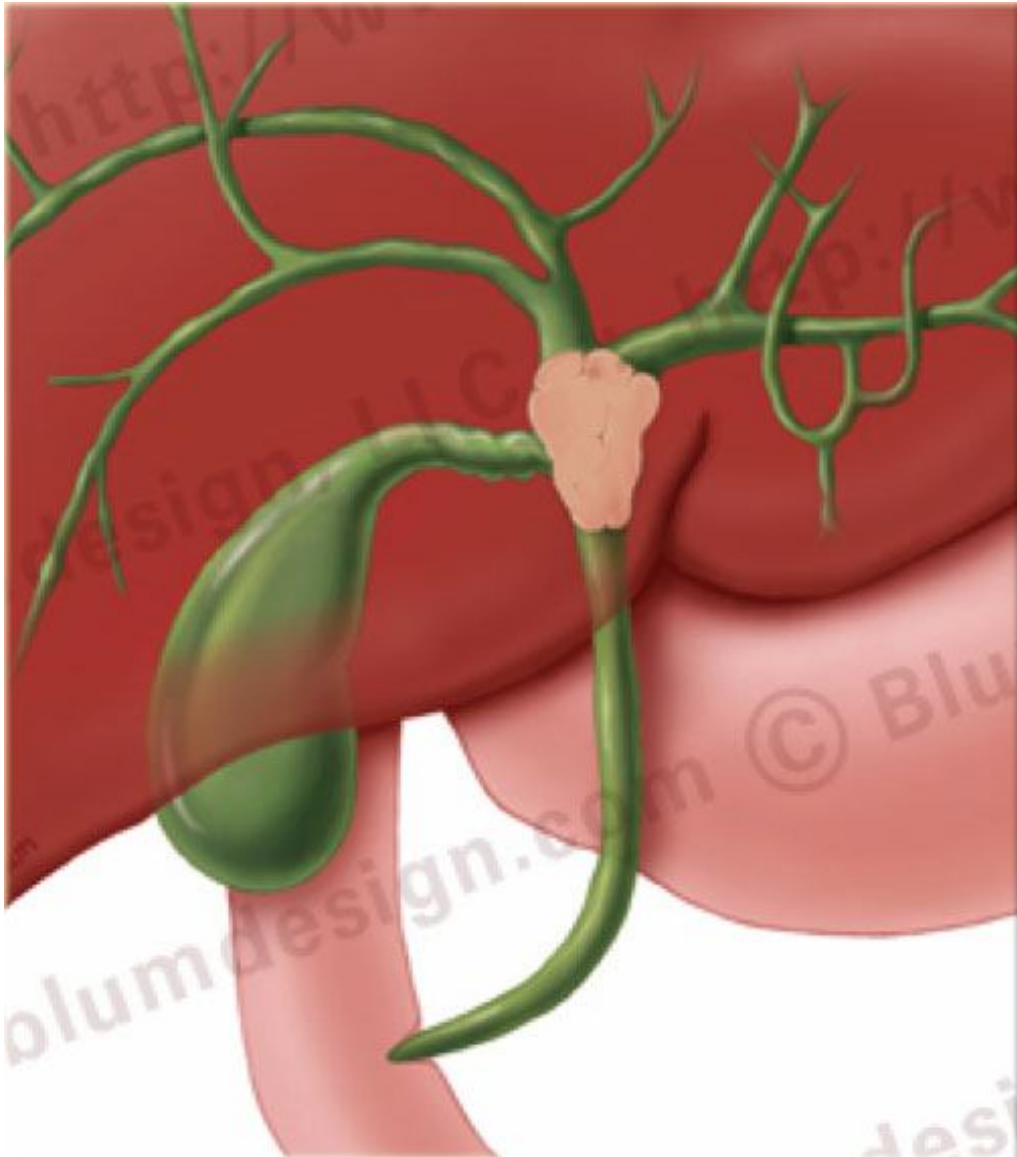
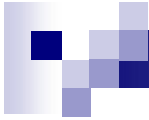
T1 Tumor involving biliary confluence ± unilateral extension to second-order biliary radicles

T2 Tumor involving biliary confluence ± unilateral extension to second-order biliary radicles *and* ipsilateral portal vein involvement ± ipsilateral hepatic lobar atrophy

T3 Tumor involving biliary confluence + bilateral extension to second-order biliary radicles; or unilateral extension to second-order biliary radicles with contralateral portal vein involvement; or unilateral extension to second-order biliary radicles with contralateral hepatic lobar atrophy; or main or bilateral portal venous involvement



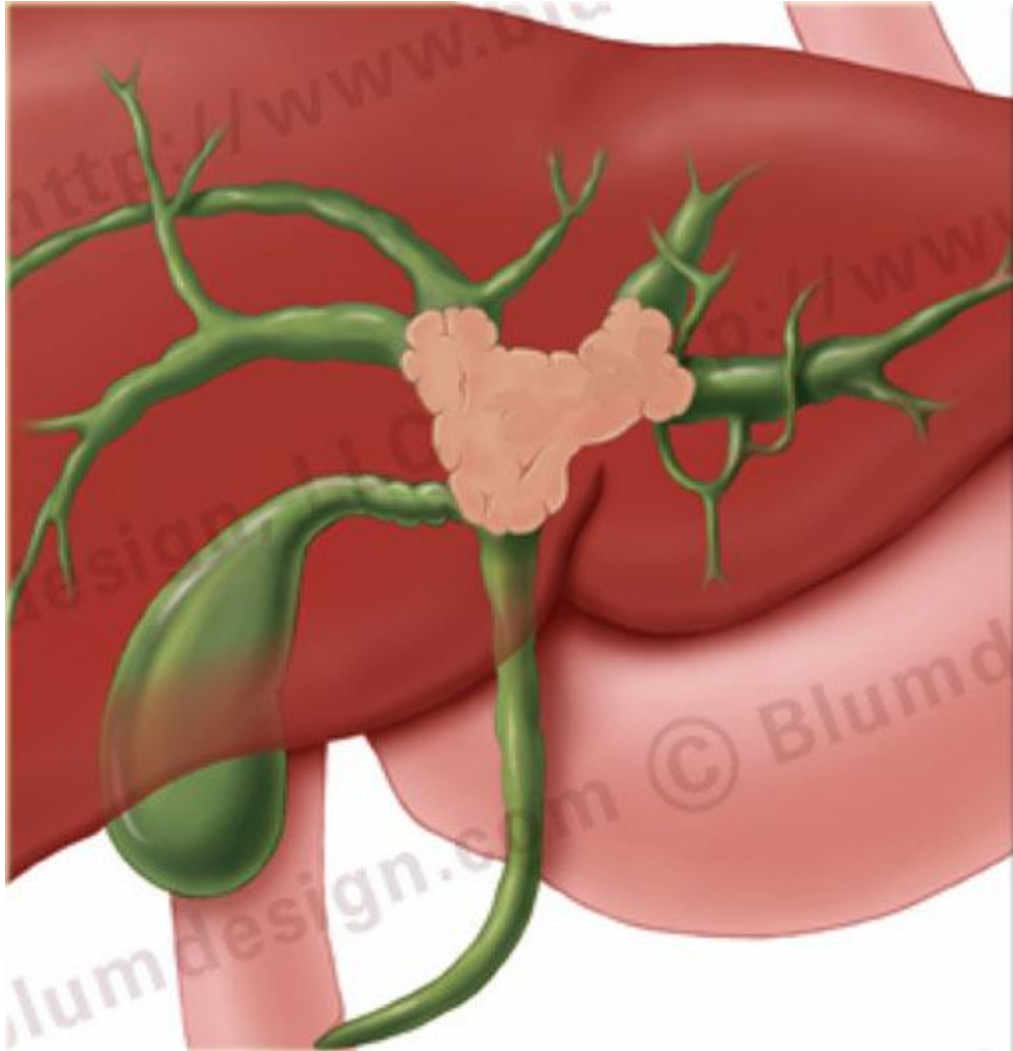
Bismuth-Corlette Type I



Bismuth-Corlette type II



Bismuth-Corlette type III



Bismuth-Corlette type IV

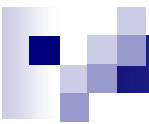


Table 1. CRITERIA OF UNRESECTABILITY

Patient Factors

Medically unfit or otherwise unable to tolerate a major operation
Hepatic cirrhosis

Local Tumor-Related Factors

Tumor extension to secondary biliary radicles bilaterally
Encasement or occlusion of the main portal vein proximal to its bifurcation
Atrophy of one hepatic lobe with contralateral portal vein branch encasement or occlusion
Atrophy of one hepatic lobe with contralateral tumor extension to secondary biliary radicles
Unilateral tumor extension to secondary biliary radicles with contralateral portal vein branch encasement or occlusion

Metastatic Disease

Histologically proven metastases to N2 lymph nodes*
Lung, liver, or peritoneal metastases

* Metastatic disease to peripancreatic, periduodenal, celiac, superior mesenteric, or posterior pancreaticoduodenal lymph nodes was considered to represent disease not amenable to a potentially curative resection. By contrast, metastatic disease to cystic duct, pericholedochal, hilar, or portal lymph nodes (i.e., within the hepatoduodenal ligament) did not necessarily constitute unresectability.



Cholangiocarcinoma

■ Resection

□ Intrahepatic

- 25% or more normal liver remnant arterial inflow, venous outflow and biliary enteric drainage
- Follow hepatectomy – anatomic or nonanatomic

□ Perihilar

- Extrahepatic biliary tree (frozen sections)
- Left or right hepatectomy
- Reconstruction

□ Extrahepatic

- Location dependent resection



Cholangiocarcinoma

■ Preoperative management

- ☐ Nutritional status
- ☐ Coagulopathy
- ☐ Cardiac, pulmonary, renal disease
- ☐ Portal vein embolization
- ☐ Staging laparoscopy +/- US

■ Biliary stenting

- ☐ Hepatic/renal dysfunction
- ☐ Complications: infectious, tumor extent



Cholangiocarcinoma

■ Palliation

- Goals: minimize symptoms, improve liver function
- Biliary stents
- Surgical bypass
 - Hepaticojejunostomy
 - Gastrojejunostomy
 - Feeding tube
- Photodynamic therapy
 - IV porphyrin followed by laser irradiation
 - Improved survival compared to stenting alone

Cholangiocarcinoma

- Outcomes: 564 patients
 - Resectability rates 30-50%
 - Mortality 4% (perihilar 5.4%)
 - Morbidity 35%
 - 5yr Survival 18%, R0 30%
 - Median survival 15 vs 20mos

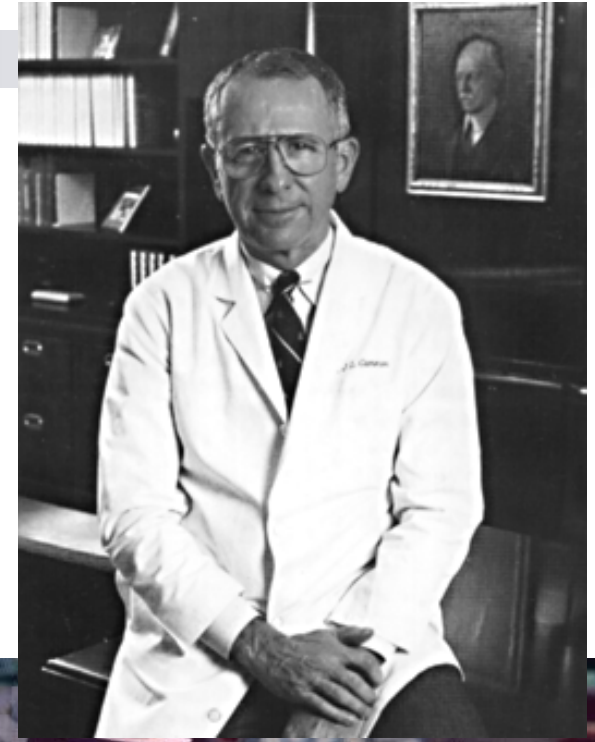


TABLE 1. Patient Characteristics, Operation Dates, Associated Diseases, Presenting Symptoms, and Preoperative Laboratory Data by Tumor Location

	Total (n = 564)	Intrahepatic (n = 44)	Perihilar (n = 281)	Distal (n = 239)	<i>P</i> *
Patient demographics					
Median age (yr)	65	60	65	68	<0.001
Sex (% male)	58	36	58	62	0.006
Race (% white)	89	91	90	89	0.50
Calendar period					
≤1989 (%)	—	4	82	14	<0.001
1989–1995 (%)	—	9	54	38	
1996–1999 (%)	—	9	31	61	
≥2000 (%)	—	9	33	58	
Associated diseases					
Stones (%)	17	11	22	16	0.21
IBD (%)	3	10	3	2	0.04
PSC (%)	2	7	3	0	0.02
Presenting symptoms					
Jaundice (%)	84	16	91	89	<0.001
Weight loss (%)	35	16	37	36	0.03
Abdominal pain (%)	30	54	32	24	<0.001
Fever (%)	9	6	14	3	<0.001
Nausea and vomiting (%)	20	5	25	12	0.001
Preoperative laboratory data					
Bilirubin (mg/dL)	5.2	1.7	5.7	5.3	0.003
Alkaline phosphatase (IU/L)	312	204	351	283	<0.001
AST (IU/L)	83	109	83	75	0.37
ALT (IU/L)	102	85	99	111	0.57
Albumin (g/dL)	3.6	3.8	3.4	3.7	<0.001

**P* values compare variables among patients with the 3 tumor locations (distal, perihilar, and intrahepatic).

IBD indicates inflammatory bowel disease; PSC, primary sclerosing cholangitis; AP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

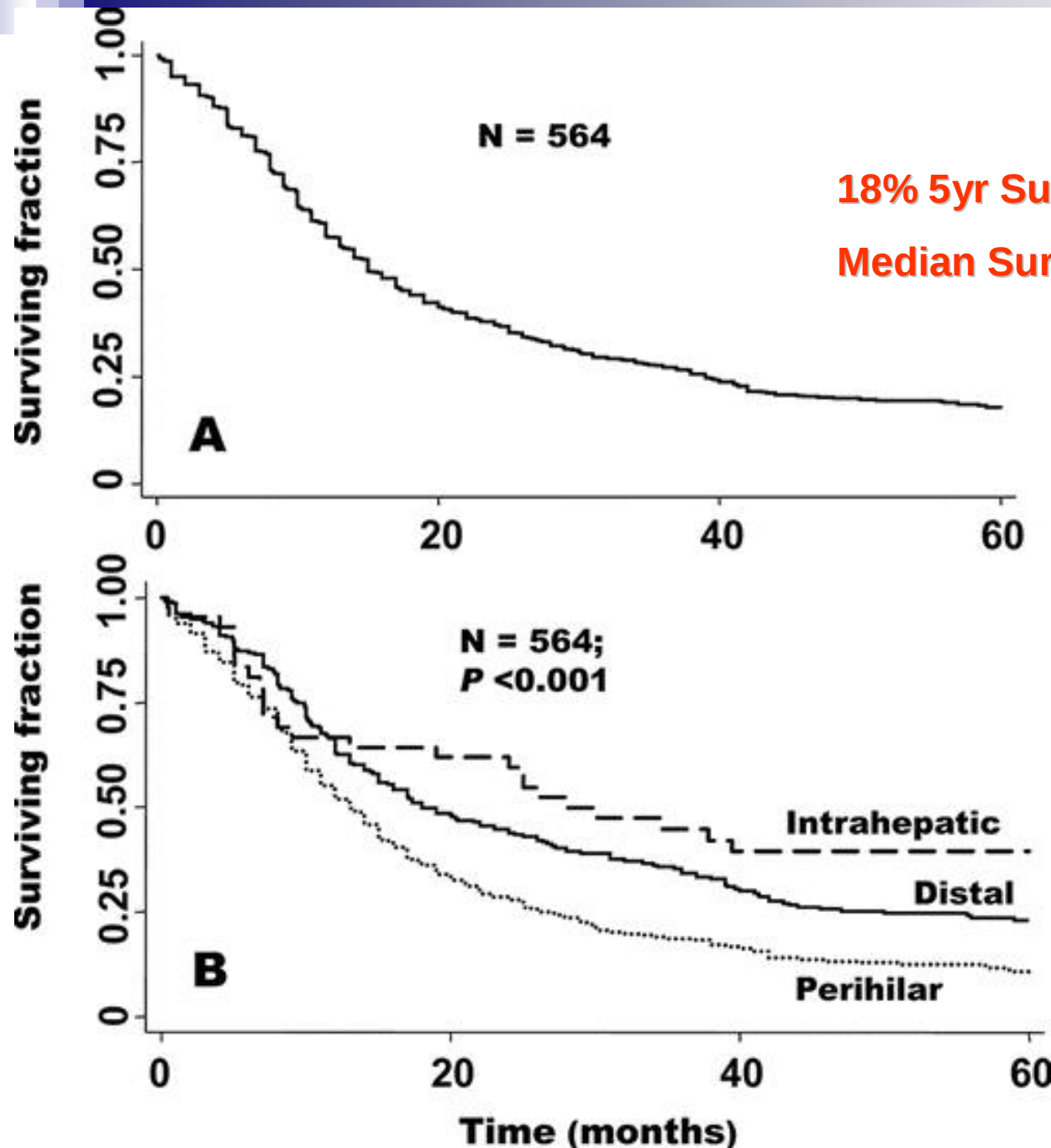


TABLE 3. Operative Procedures, Postoperative Complications, and Median Survival by Tumor Location

	Total (n = 564)	Intrahepatic (n = 44)	Perihilar (n = 281)	Distal (n = 239)	<i>P</i>*
Resected (%)	76	66	62	96	<0.001
Postoperative complications					
Wound infection (%)	13	5	16	11	0.05
Bile leak (%)	4	0	7	1	<0.001
Pancreatic leak (%)	5	0	0	13	<0.001
Abscess (%)	8	9	8	7	0.68
Sepsis (%)	6	5	10	3	0.004
DGE (%)	5	0	2	10	<0.001
Respiratory (%)	4	7	5	4	0.48
Cardiac (%)	3	2	4	3	0.94
GI bleeding (%)	3	0	5	2	0.10
Renal (%)	2	2	3	2	0.69
MOSF (%)	1	5	2	0	0.08
Operative mortality (%)	4	4	5	3	0.41
Median survival (mo)	15	25	14	18	<0.001

**P* values compare variables among patients with the 3 tumor locations (distal, perihilar, and intrahepatic).

GI indicates gastrointestinal; DGE, delayed gastric emptying; MOSF, multiple-organ system failure.



18% 5yr Survival (R0 30%)

Median Survival 15months (R0 28mos)

40%, 28mos (R0 63%, 80mos)

23%, 18mos (R0 30%, 30mos)

10%, 13mos (R0 27%, 25mos)

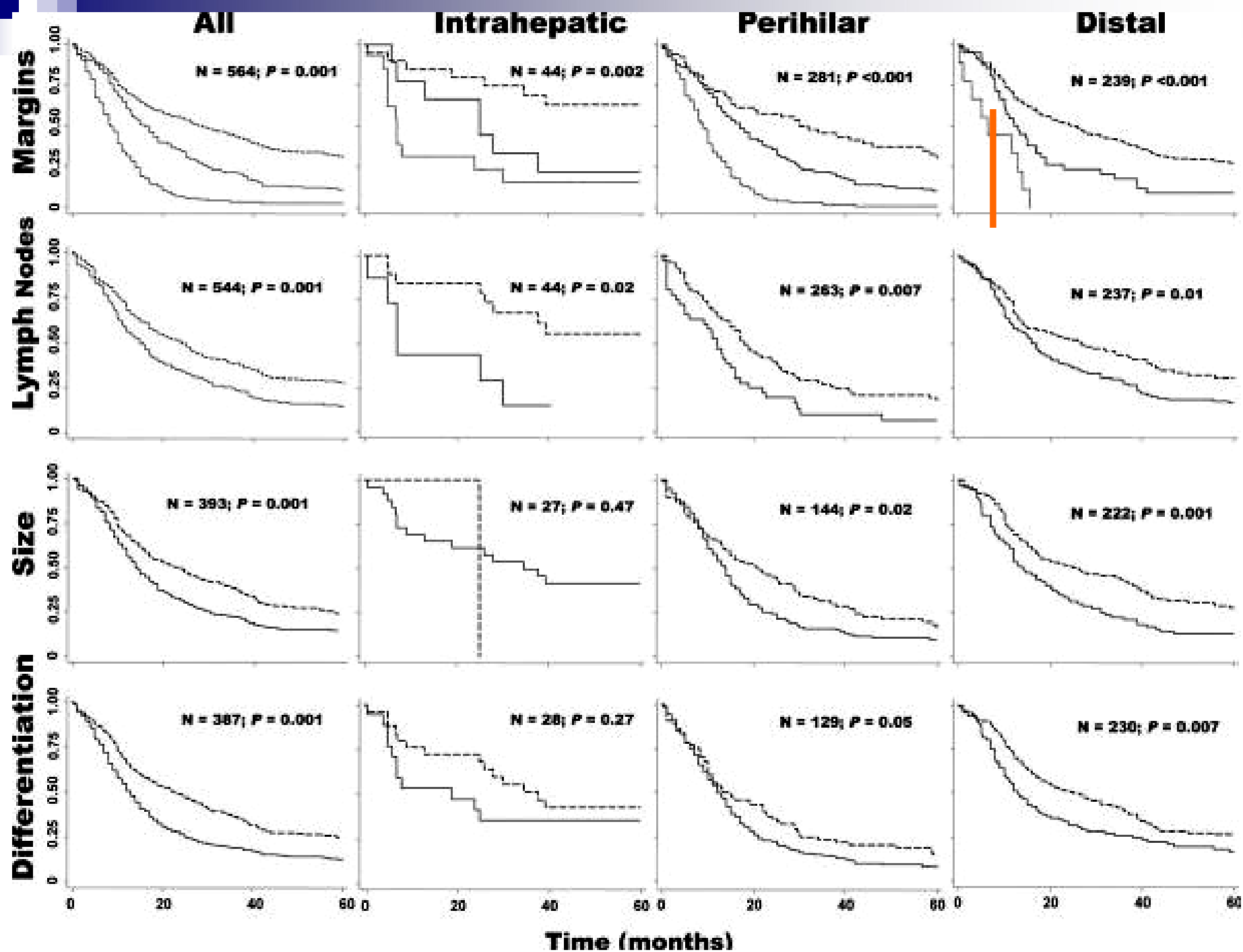


TABLE 5. Comparison of Recent Series

Reference (year)	Resected (N)	Liver Resection (%)	5-Year Survival, R0 (%)	5-Year Survival, All (%)	Mortality (%)
Intrahepatic					
Pichlmayr (1995) ¹¹	32	100	NR	17	6
Jan (1996) ¹²	41	100	44	27	0
Casavilla (1997) ¹³	34	100	NR	31	7
Lieser (1998) ³⁰	32	100	45	NR	NR
Madariaga (1998) ⁵	34	100	51	35	6
Valverde (1999) ¹⁴	30	100	NR	22	3
Inoue (2000) ¹⁵	52	100	55	36	2
Weber (2001) ¹⁶	33	100	NR [†]	31	3
Present series	34	100	63	40	2
Perihilar					
Suigura (1994) ¹⁷	83	100	33	20	8
Su (1996) ¹⁸	49	50	34	15	10
Nagino (1998) ¹⁹	138	90	26	NR	10
Miyazaki (1998) ²⁰	76	86	40	26	15
Madariaga (1998) ⁵	28	100	25	9	14
Kosuge (1999) ⁷	65	80	52	35	9
Neuhaus (1999) ²¹	95*	85	37	22	6
Jarnagin (2001) ²²	80	78	30	NR	10
Kondo (2004) ²³	40	78	NR [‡]	NR	0
Rea (2004) ²⁴	46	100	30	26	9
Nishio (2005) ²⁵	301	95	27	22	8
Dianant (2006) ²⁶	99	38	33	27	15
Wahab (2006) ²⁷	73	100	NR	13	11
Present series	173	20	30	10	5
Distal					
Bortolasi (2000) ²⁸	15	0	NR	20	0
Yoshida (2002) ²⁹	27	0	44	37	4
Present series	229	0	27	23	3

*Includes 15 hepatectomies with liver transplantation.

[†]Three-year survival = 62%.[‡]Three-year survival = 44%.

NR indicates not reported; JHMI, Johns Hopkins Medical Institutions.



What's changed in the last 30yrs

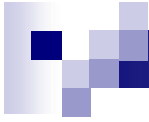
- Hilar cholangiocarcinoma (Klatskin tumor)

- Advances in perioperative staging
- 30 – 50% LN positive on resection
- Improved outcomes
 - 25 – 40% 5yr survival
 - 50 – 75% recurrence (12 - 43 months)
- Liver resection (caudate)
 - Improved outcome, DFS
 - Unknown benefit for B-C I and II
- Liver transplantation (Mayo Protocol)
 - Portal v, bilateral hepatic duct involvement
 - Locally advanced without nodal involvement



Denver contribution

- Phase I trials for gerfitinib, capecitabine, celecoxib
- Recurrent PSC following liver transplantation
- Basic science contributions



Conclusion

- Cholangiocarcinoma is rare (3%)
- Intrahepatic, Perihilar, Extrahepatic
- 50% resectability
- Best outcome with R0 resection
- Poor response to chemo/xrt





Thank you

References

- Martin II, RCG, Vitale, GC, Reed Jr, DN, Larson, GM, Edwards, MJ, McMasters, KM. Surg Endosc (2002) 16: 667-70
- Mann, CD, Thomasset, SC, Johnson, NA, Garcea, G, Neal, CP, Dennison, AR, Berry, DP. ANZ J Surg (2009) 471 – 75.
- DeOliveira, ML., Cunnigham, SC., Cameron, JL., Kamangar, F., Winter, JM., Lillemoe, KD., Choti, MA., Yeo, CJ., Schulick, RD. Ann Surg (2007). 245(5): 755 – 62.
- Nguyen, KT., Steel, J., Vanounou, T., Tsung, A., Marsh, JW., Geller, DA., Gamblin, TC. Ann Surg Onc. (2009) 16: 3308 – 15.
- Ito, F., Cho, CS., Rikkers, LF., Weber, SM. Ann Surg (2009) 250(2): 210 – 18.
- Hueman, MT., Voller Jr, CM., Pawlik, TM. Ann Surg Onc (2009) 16: 2101 – 2115.
- Jarnagin, WR., Fong, Y., DeMatteo, RP. Ann Surg (2001). 234: 507 – 17.

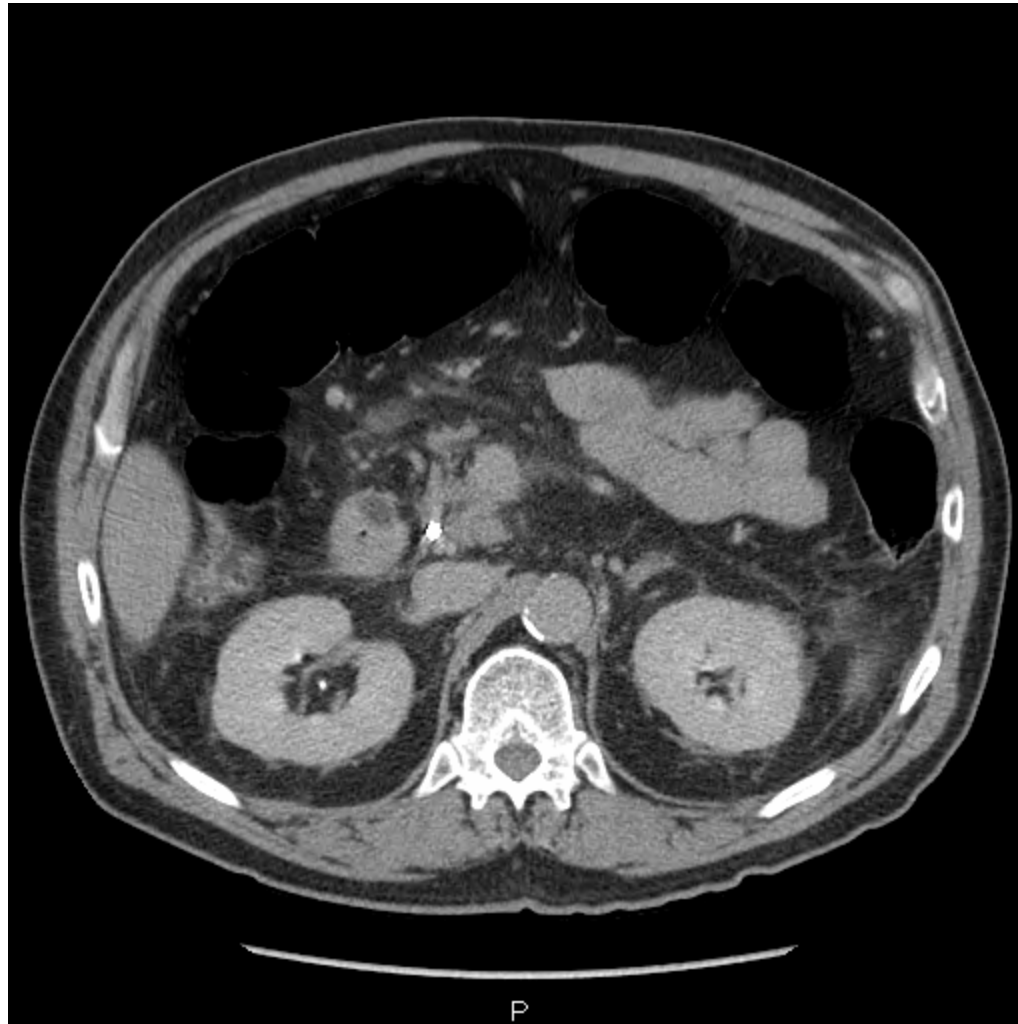


Image 397 10/23/09

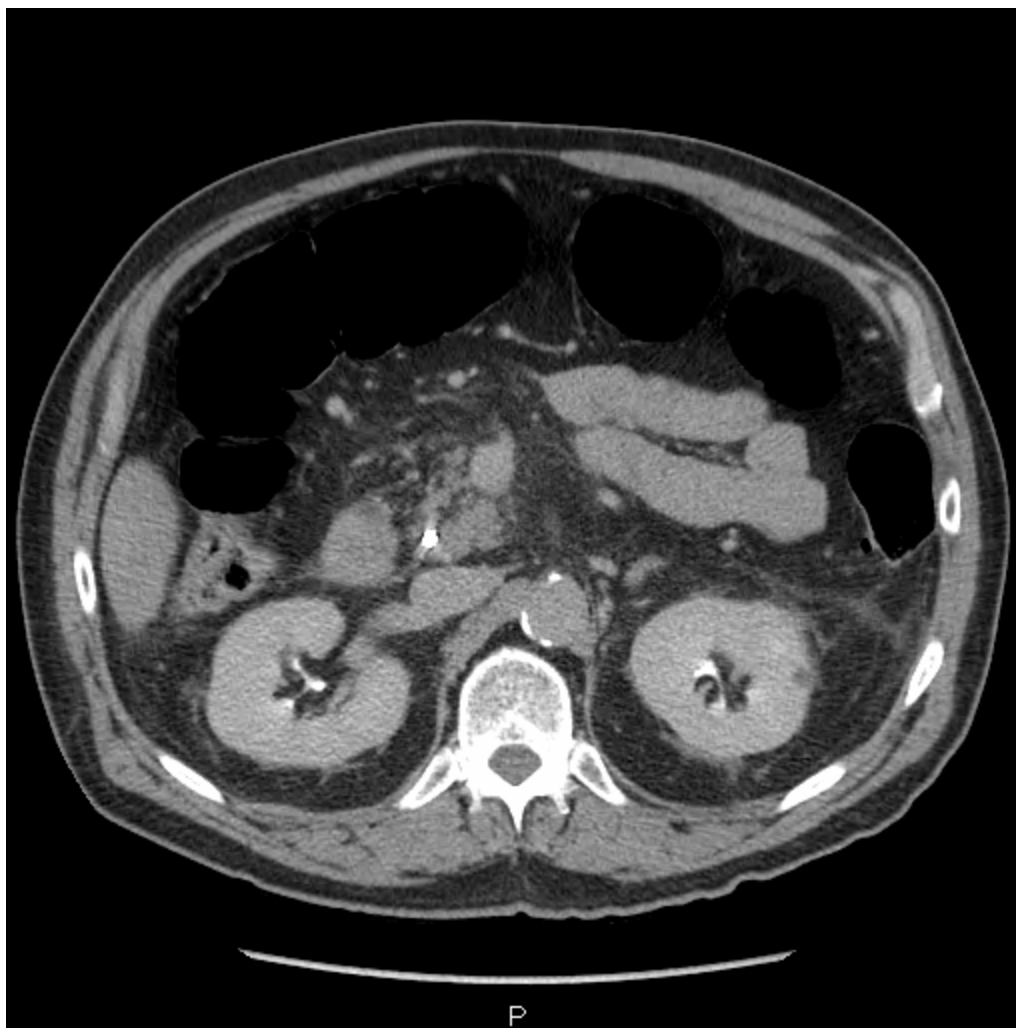


Image 394 10/23/09

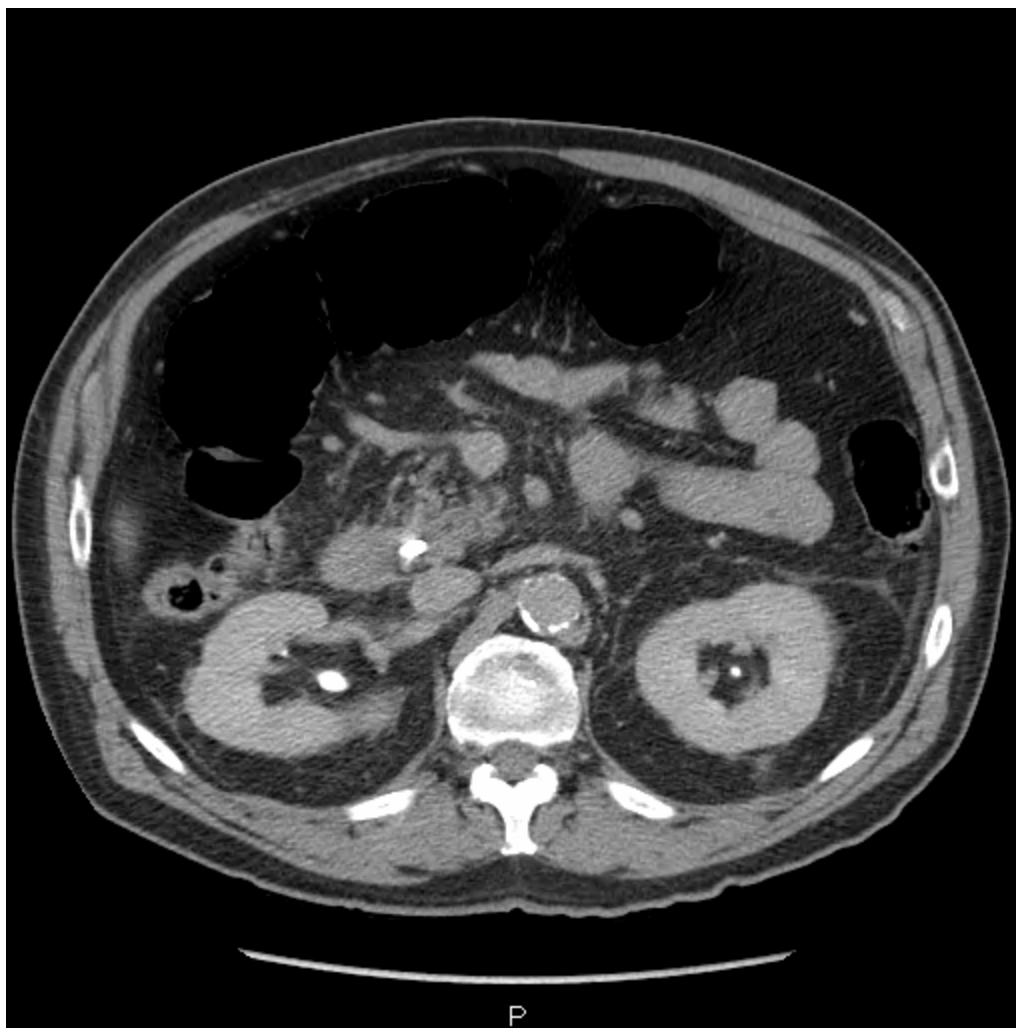


Image 389 10/23/09

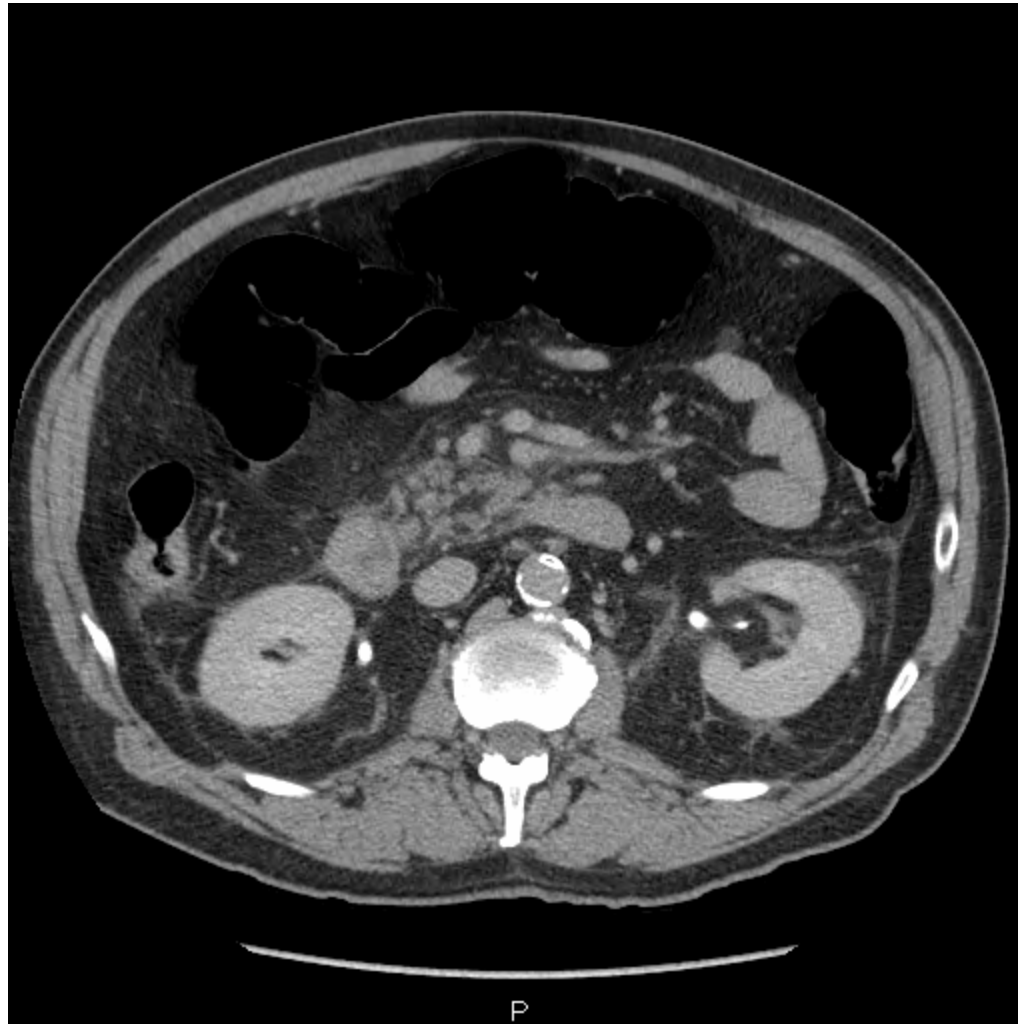
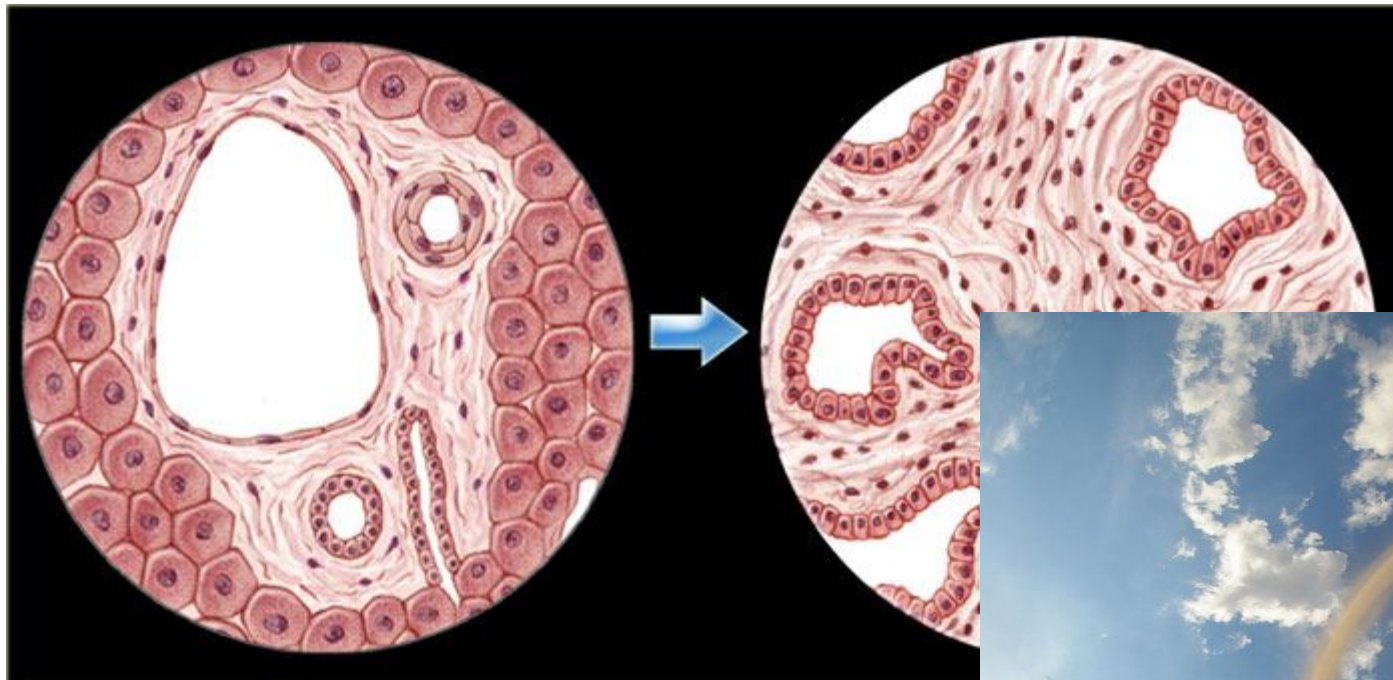
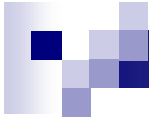
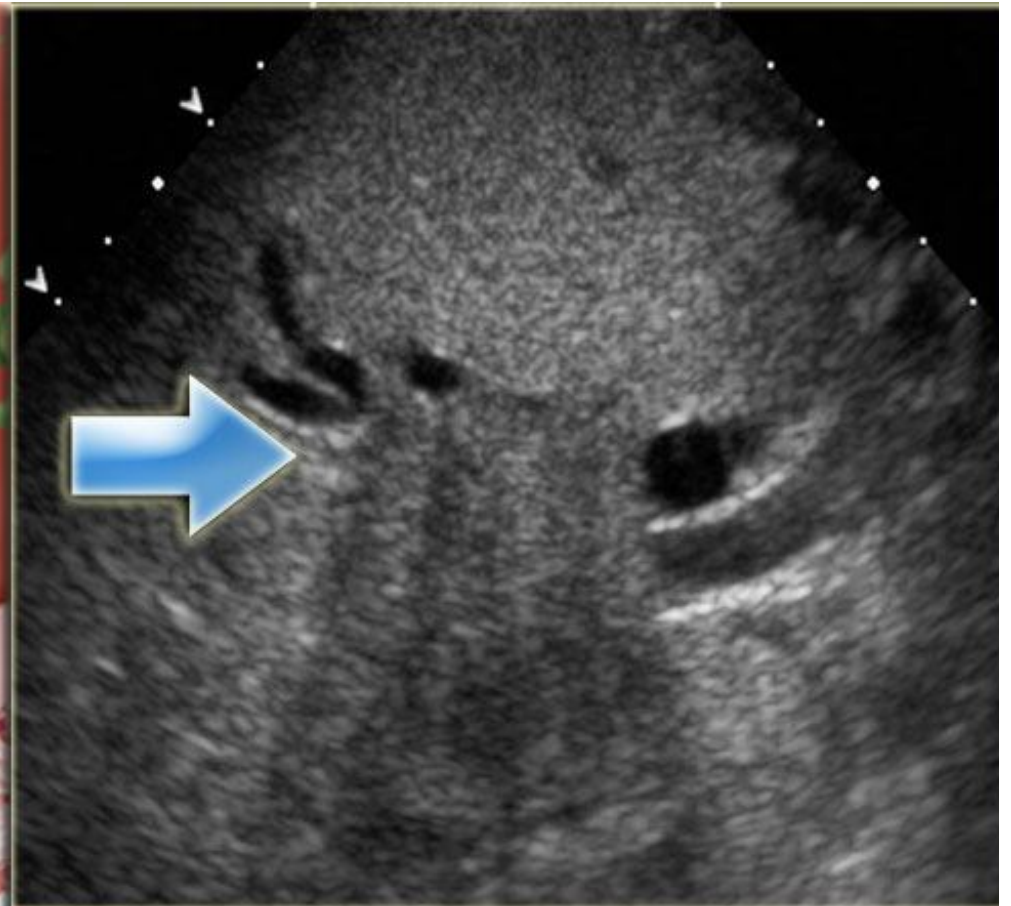
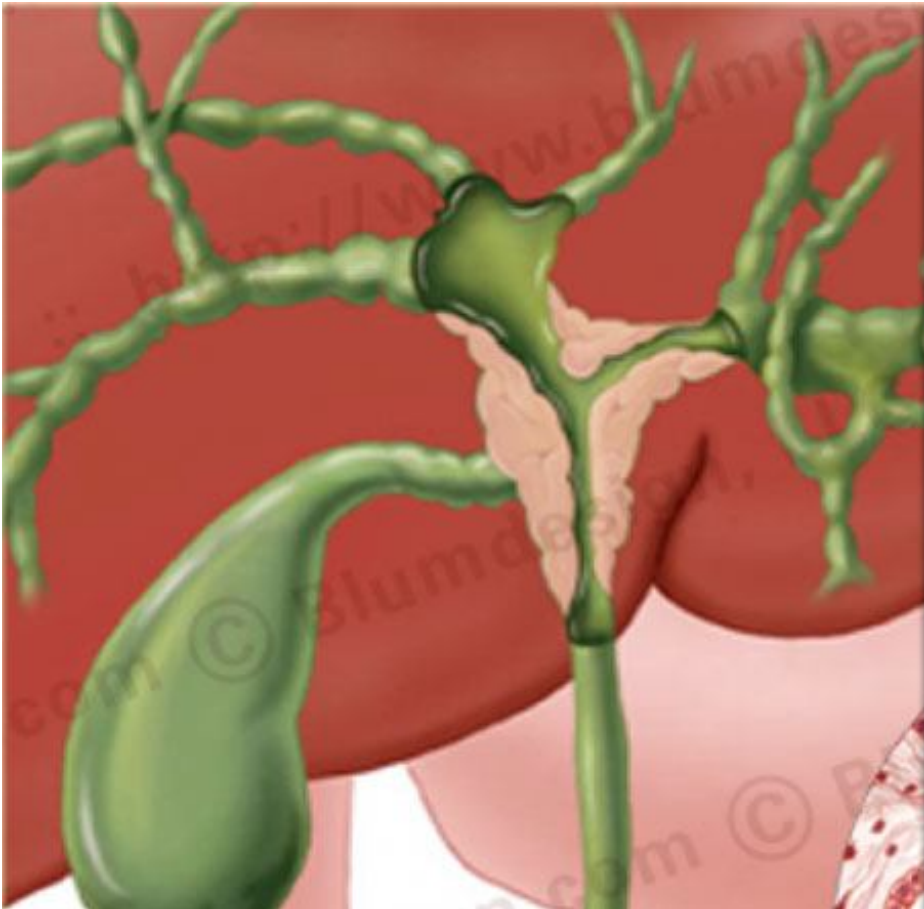
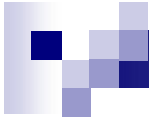


Image 383 10/23/09

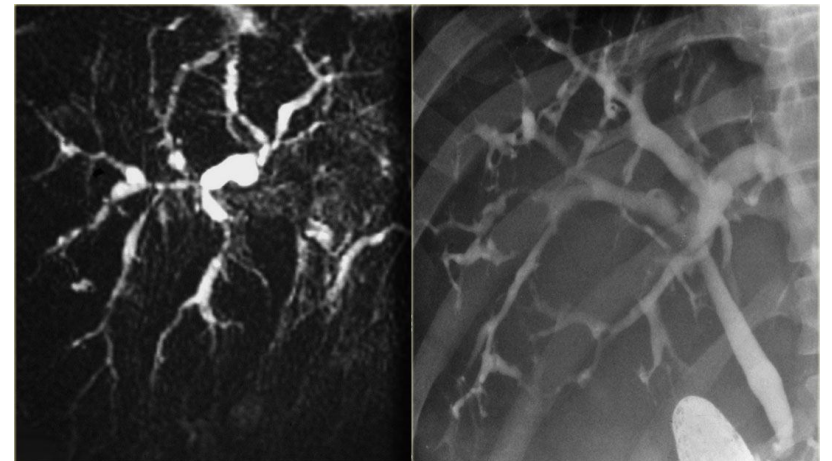


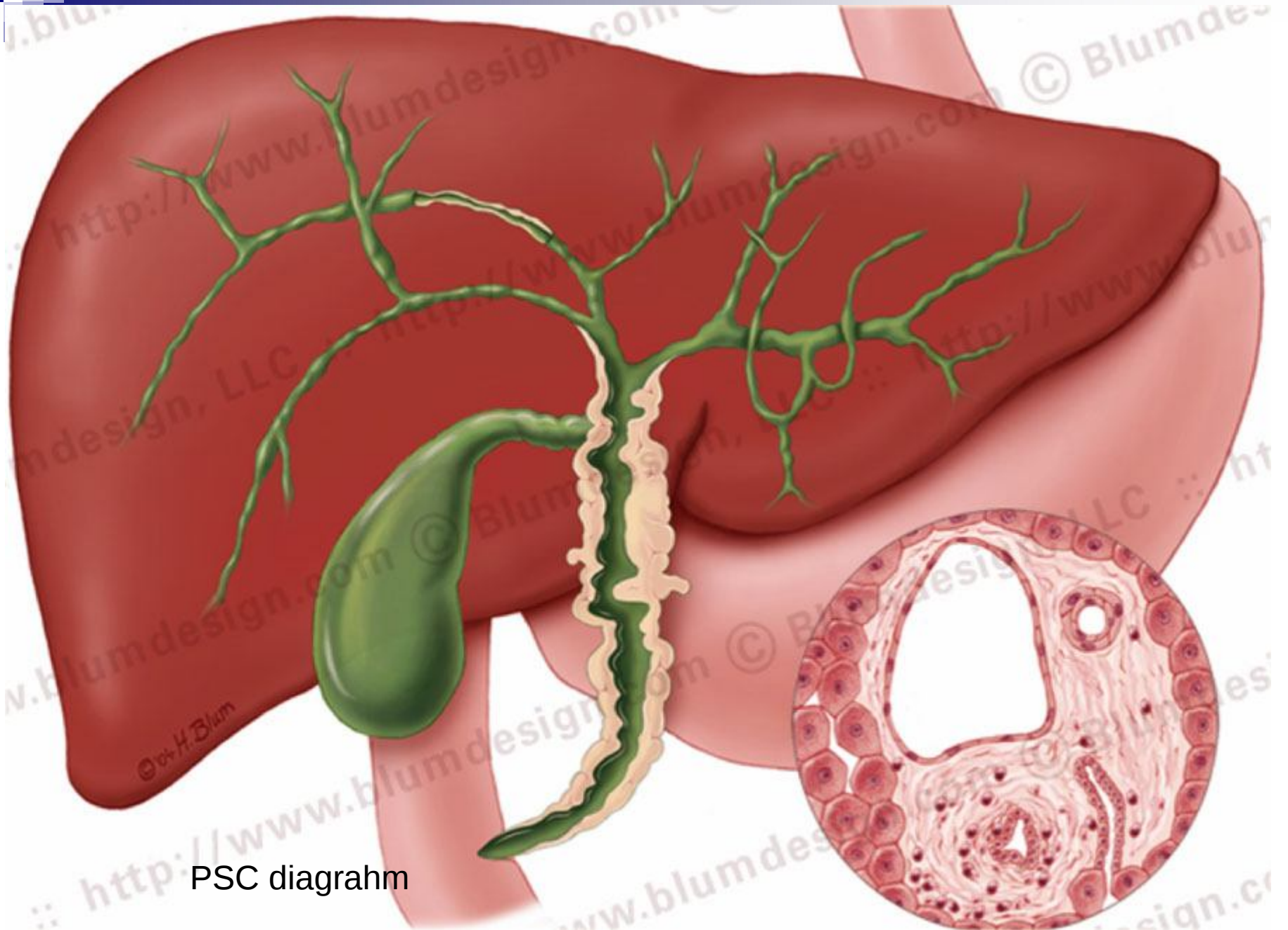
Klatskin tumor



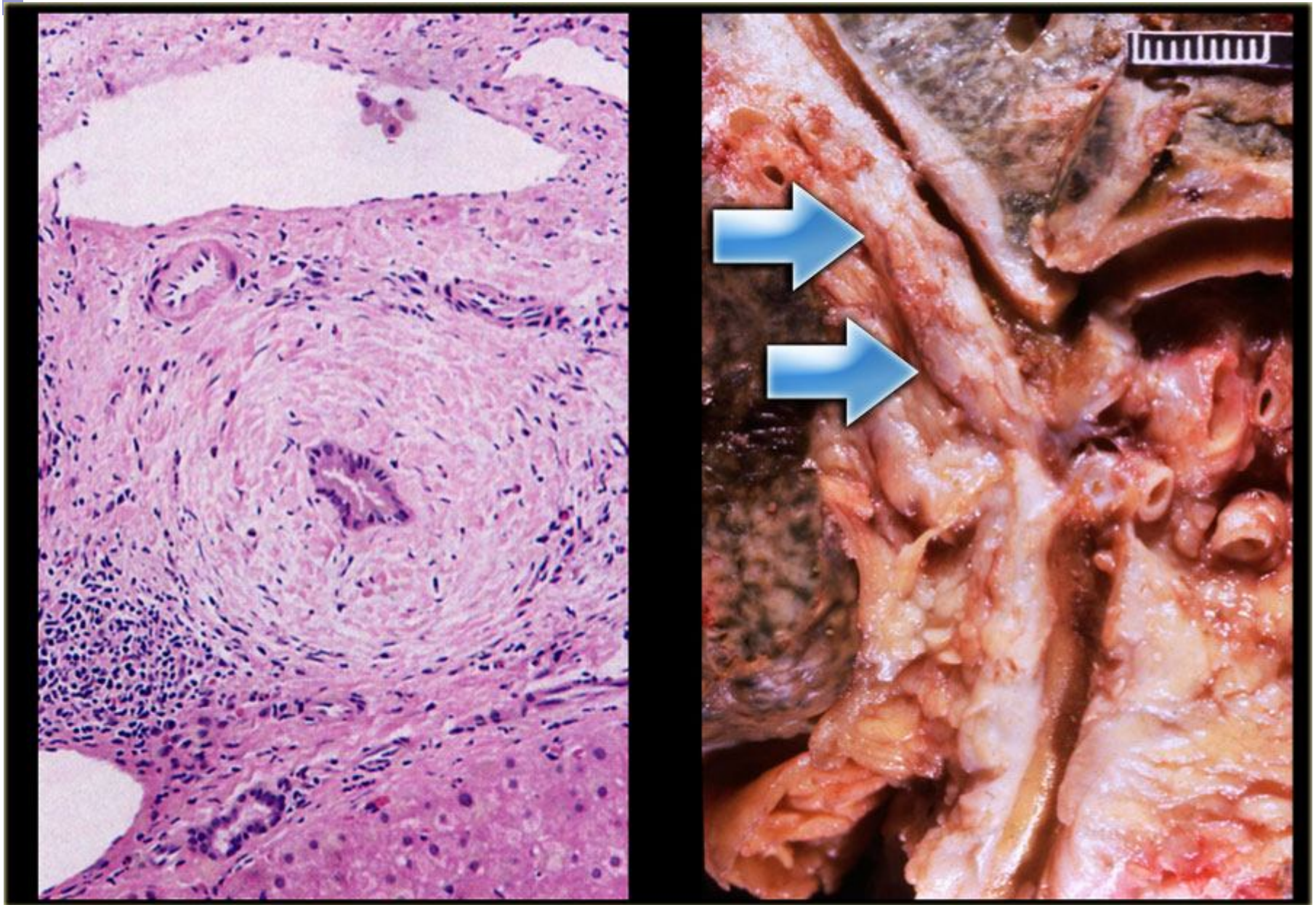


PSC ERCP





PSC diagram



PSC path





Cholangiocarcinoma

■ Unresectability

- ☐ Hepatic duct involvement up to secondary biliary radicals bilaterally
- ☐ Encasement or occlusion of the main portal vein proximal to its bifurcation
- ☐ Atrophy of one hepatic lobe with contralateral involvement of secondary biliary radicals
- ☐ Unilateral tumor extension to secondary biliary radicals with contralateral vein branch encasement or occlusion

- ☐ Evidence of metastatic disease

Imaging: Cat Scan

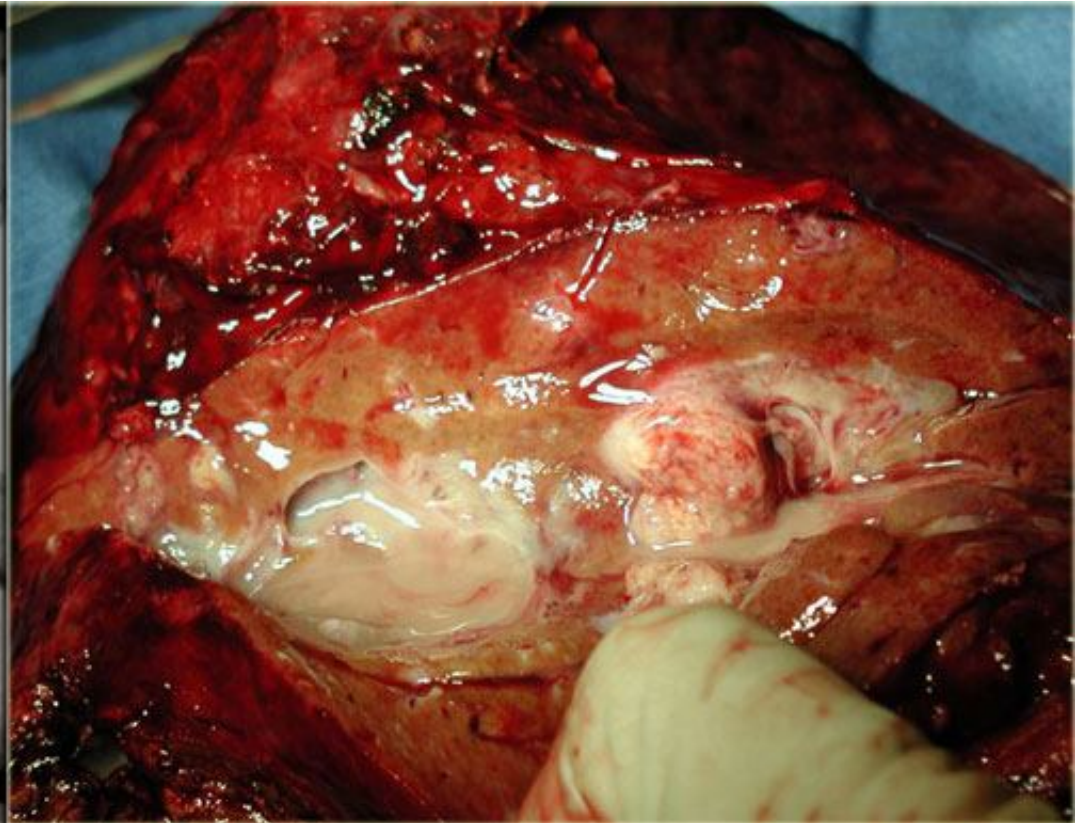
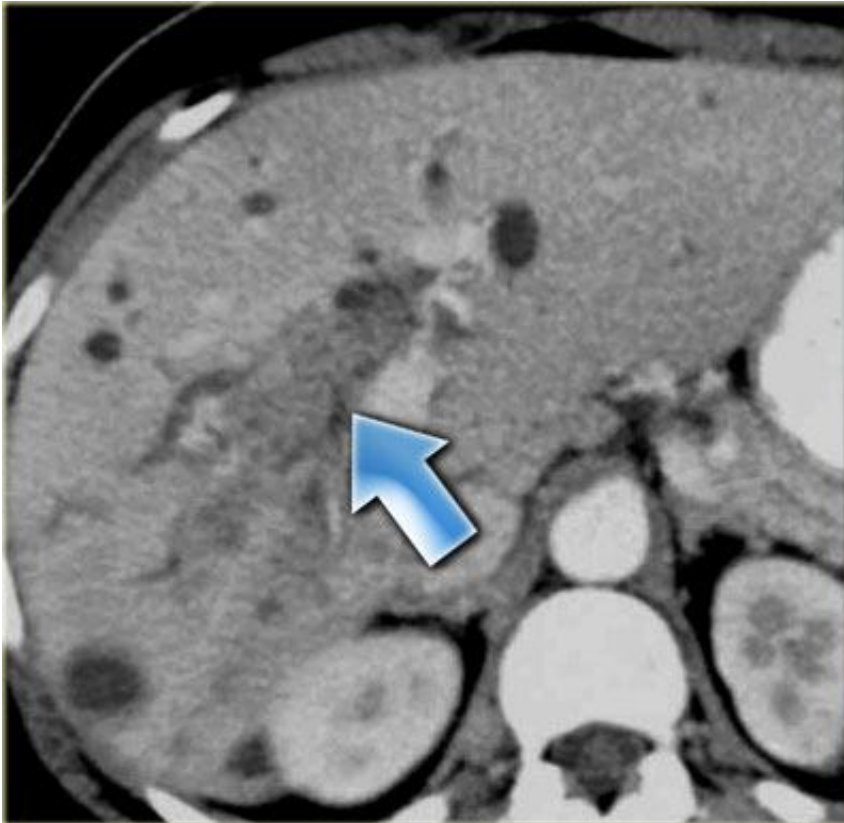




Table 2. PROPOSED T-STAGE CRITERIA FOR HILAR CHOLANGIOCARCINOMA

Stage	Criteria
T1	Tumor involving biliary confluence +/- unilateral extension to second-order biliary radicles
T2	Tumor involving biliary confluence +/- unilateral extension to second-order biliary radicles and ipsilateral portal vein involvement +/- ipsilateral hepatic lobar atrophy
T3	Tumor involving biliary confluence + bilateral extension to second-order biliary radicles; or unilateral extension to second-order biliary radicles with contralateral portal vein involvement; or unilateral extension to second-order biliary radicles with contralateral hepatic lobar atrophy; or main or bilateral portal venous involvement