E-AHPBA Postgraduate course, MUMC 2016

BILIARY TRACT TUMORS

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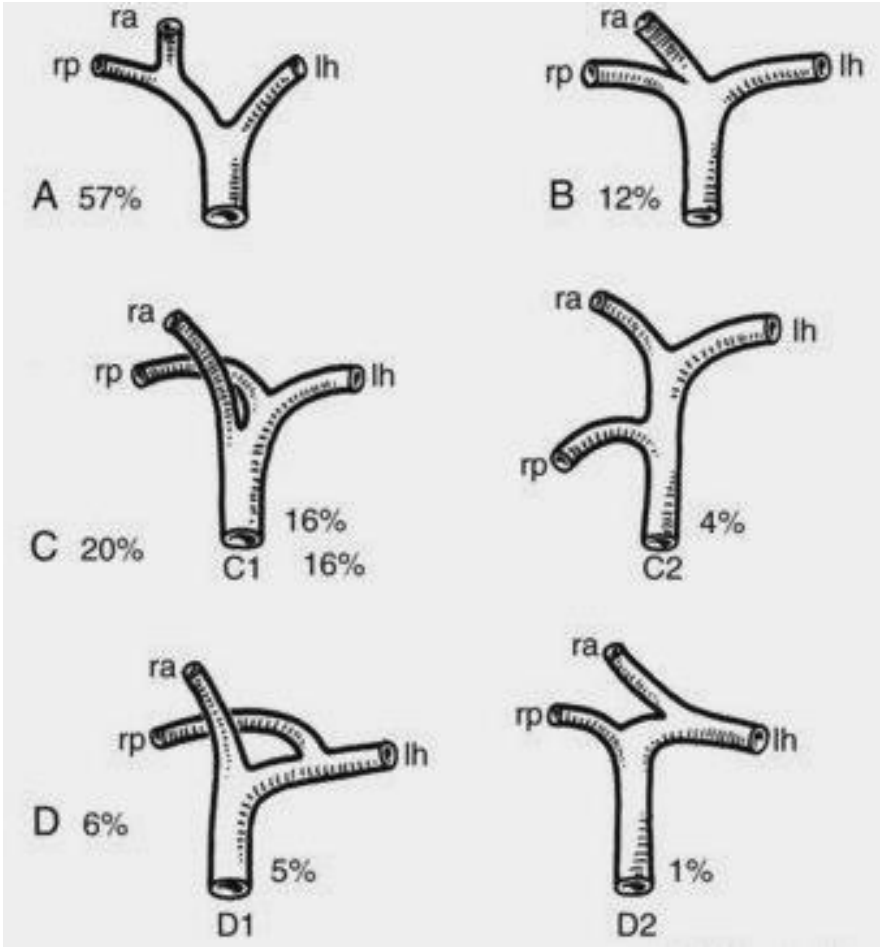
DISCLOSURE

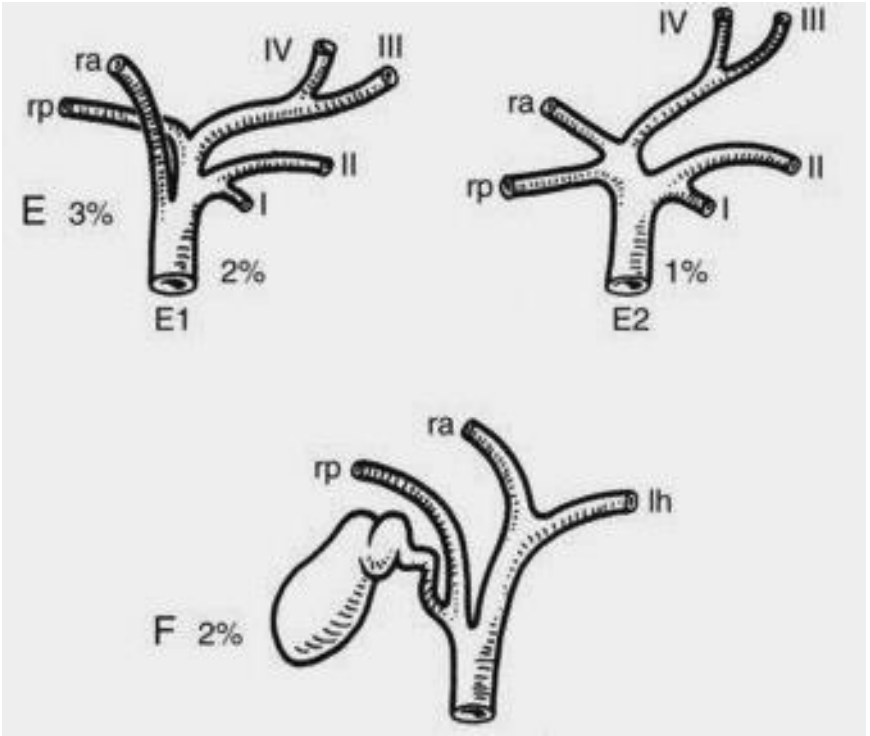
- Nothing to disclose.

BILIARY TUMORS - OVERVIEW

- Biliary anatomical variations
- Classification
- Intrahepatic cholangiocarcinoma
- Perihilar cholangiocarcinoma
- Gallbladder cancer
- Systemic therapy
- Intraductal Papillary Neoplasm of the Bile duct (IPNB)
- Gallbladder polyp

BILIARY ANATOMICAL VARIATIONS





BILIARY TUMORS - CLASSIFICATION

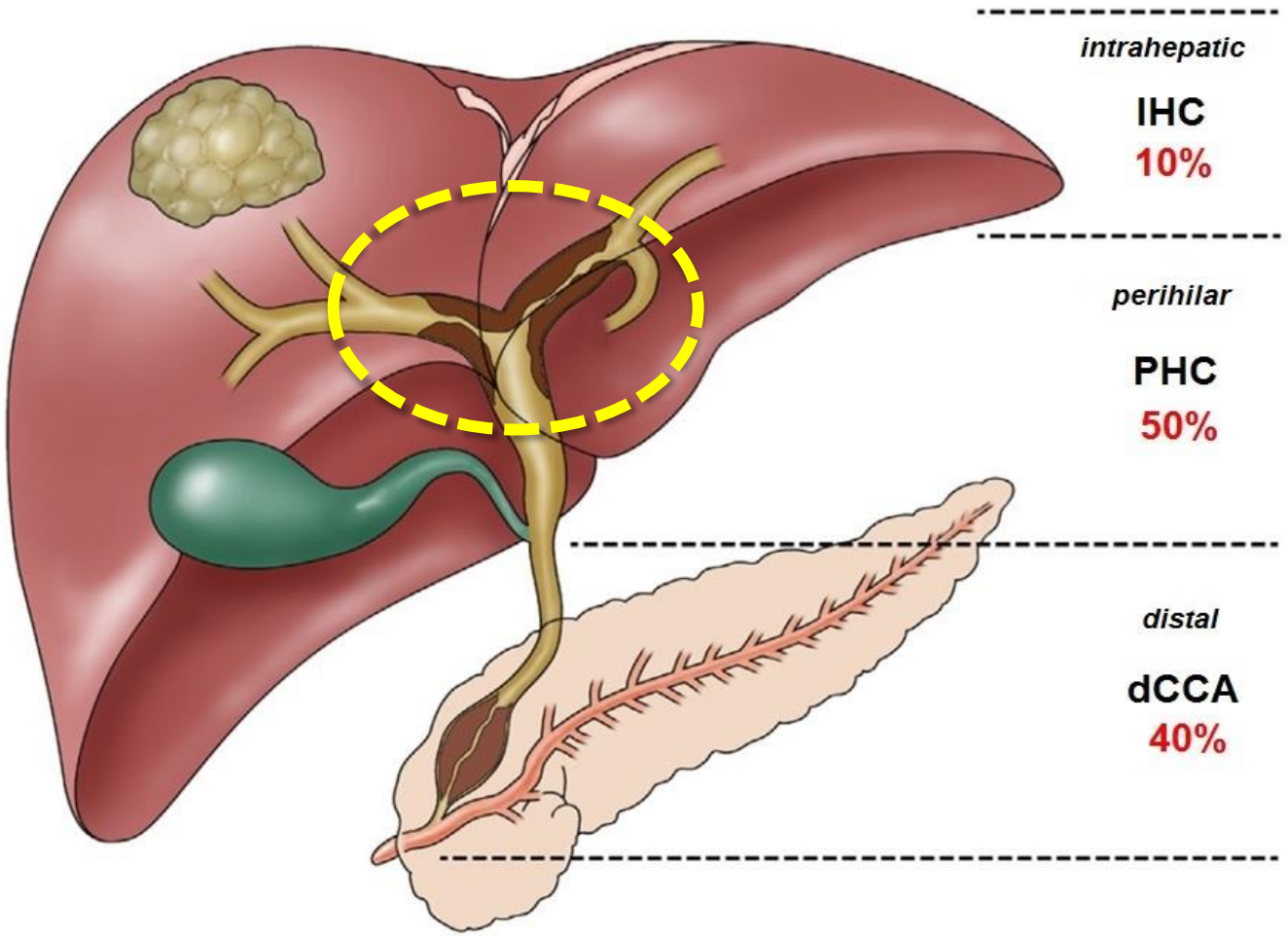
Gallbladder cancer

- Including cancer arising from cystic duct

Cholangiocarcinoma

- AJCC 6th edition: intra- vs extrahepatic
- AJCC 7th edition: intrahepatic, perihilar, distal
- Intrahepatic: proximal to second-order bile duct
- Distal: distal to origin cystic duct
- Perihilar: in between second-order bile duct and cystic duct

BILIARY TUMORS



INTRAHEPATIC - DIAGNOSIS

- Incidence 1:100,000, about 5,000 annually in EU; increasing
- RF similar to HCC: cirrhosis, viral hepatitis, alcohol, DM
- Symptoms: weight loss, malaise, abdominal discomfort
- Tumor markers: 50% CA19-9 >100
- CT: large irregular hypo-intense mass on non-contrast, peripheral enhancement in arterial phase, progressive enhancement in venous phase
- Subtypes: mass-forming (85%), intra-ductal, periductal
- Rule out metastatic disease (CRC, gastric, breast)
- Biopsy not required

INTRAHEPATIC - STAGING

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ (intraductal tumor)
T1	Solitary tumor without vascular invasion
T2a	Solitary tumor with vascular invasion
T2b	Multiple tumors, with or without vascular invasion
T3	Tumor perforating the visceral peritoneum or involving the local extra hepatic structures by direct invasion
T4	Tumor with periductal invasion

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
Stage IVA	T4	N0	M0
	Any T	N1	M0
Stage IVB	Any T	Any N	M1

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De Jong, JCO 2011;29:3140

INTRAHEPATIC - RESECTION

Only if:

1. Complete resection feasible, considering liver function
2. Resection likely to improve survival
3. Acceptable mortality risk

Unfavorable risk factors:

- Multiple tumors – multifocal, intrahepatic mets, satellites
- Vascular invasion
- Perforation visceral peritoneum (T3=stage III)
- Nodal metastasis (N1=stage IV)

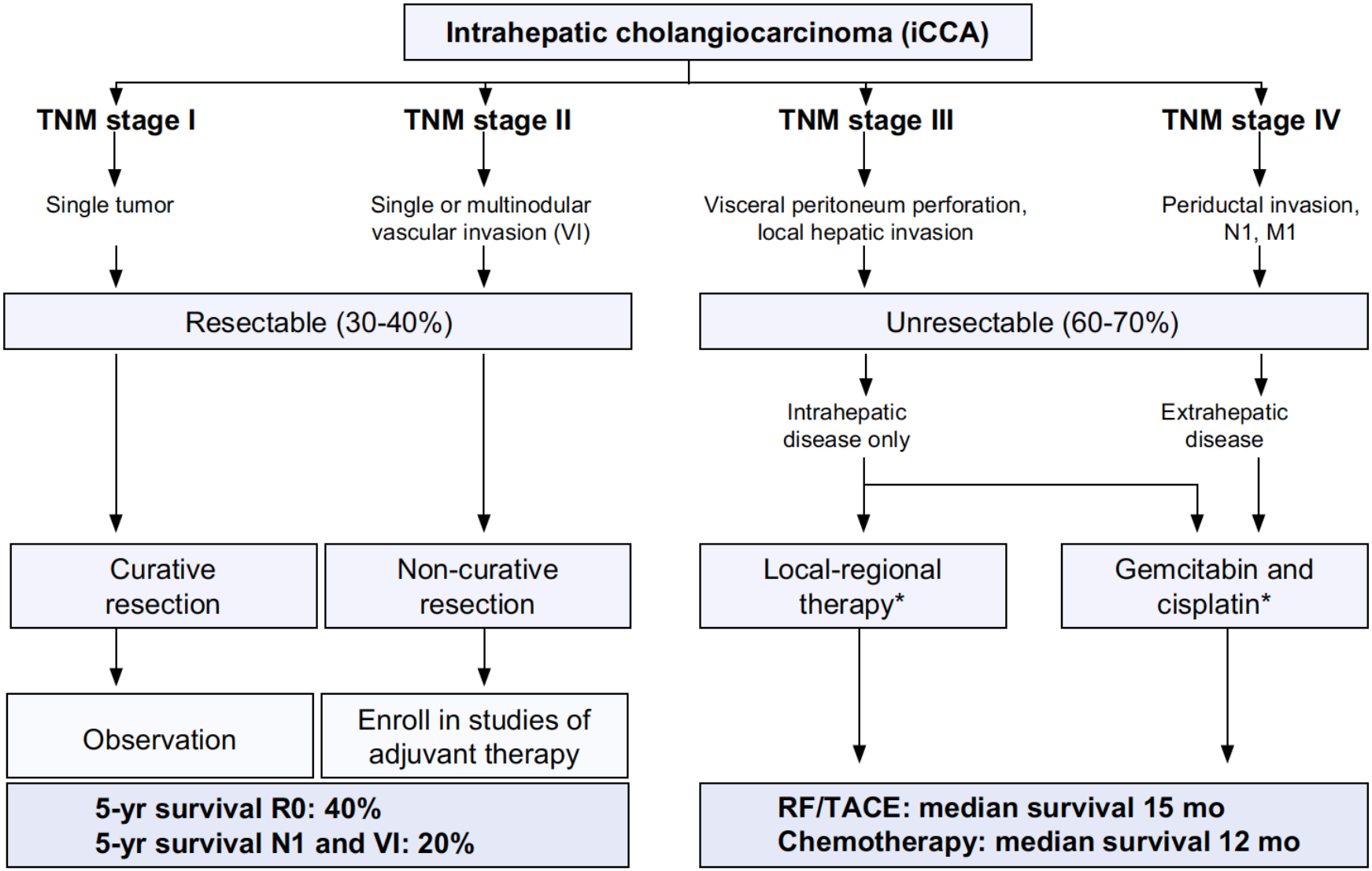
INTRAHEPATIC - RESECTION

- 30-40% resectable; 15% resected in SEER
- Staging laparoscopy uncertain benefit.
- 75% at least 4 segments resected
- 25% hepaticojejunostomy
- Lymphadenectomy of regional nodes recommended for prognostic value.
- No adjuvant therapy. Ongoing trials: e.g., ACTICCAA.

INTRAHEPATIC - OUTCOMES

- Mortality 1-5% in high-volume center; higher if cirrhosis, extended resection, or biliary drainage and reconstruction.
- Median RFS 20 months; 60% intrahepatic only, 20% extrahepatic only, 20% both[1]
- Median OS 30 months with 5-year OS 32%, averaged over large series[2]
- Liver transplant: similar to HCC if solitary <2cm in cirrhotic[3]
- Several prognostic scores outperform AJCC; additional postoperative poor prognostic factors are positive margin and poor tumor differentiation.
- Presence of multiple RF does not preclude 5-year OS.

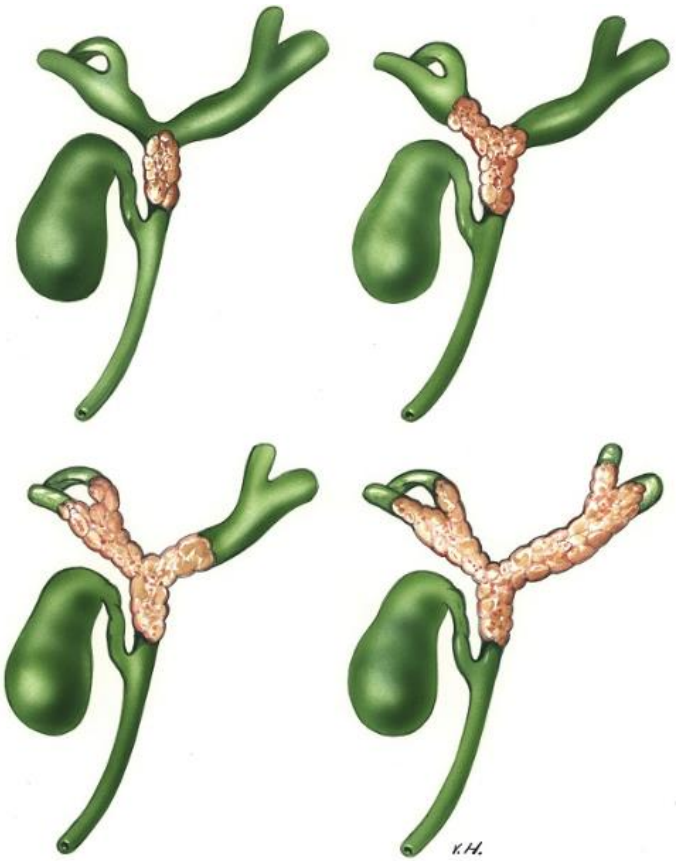
[1]Hyder, Surgery 2013;153:811
[2]Groot Koerkamp, JSO 2014;110:585
[3]Sapisochin, AnnSurg 2014;259:944



Bridgewater, J. Hepatology 2014;60:1268
Konstantinidis, Cancer 2016;122(5):758

PERIHILAR - DIAGNOSIS

- Incidence 2:100,000, about 10,000 in EU
- Presentation: painless jaundice (80%)
- CT: small perihilar mass with biliary dilatation, PV involvement with atrophy
- Hilar nodes (N1) are stage IIIB
- Biliary extent: Bismuth classification
- PV and HA involvement
- Brush cytology has low yield
- Biopsy not required



PERIHILAR - STAGING

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue
T2a	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue
T2b	Tumor invades adjacent hepatic parenchyma
T3	Tumor invades unilateral branches of the portal vein or hepatic artery
T4	Tumor invades main portal vein or its branches bilaterally; or the common hepatic artery; or the second-order biliary radicals bilaterally; or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a-b	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T1-3	N1	M0
Stage IVA	T4	N0-1	M0
Stage IVB	Any T	N2	M0
	Any T	Any N	M1

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PERIHILAR – DRAINAGE, PVE

- Biliary drainage of future liver remnant (FLR) to decrease liver failure risk.
- EBD: more cholangitis, more interventions
- PTCD: risk of peritoneal seeding
- FLR>50%: consider resection without drainage[1]
- FLR <40%: consider PVE, drawback: you have to commit to left- or right-sided resection

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[1]Wiggers, JACS 2016 Apr 2

PERIHILAR - RESECTION

- Staging laparoscopy: 25% mets
- Staging laparotomy: up to 50% unresectable
- Caudate lobectomy
- Hilar lymphadenectomy
- PV reconstruction may be necessary
- No-touch technique with default PV resection and reconstruction debated
- HA reconstruction debated; increased postoperative mortality and poor biology

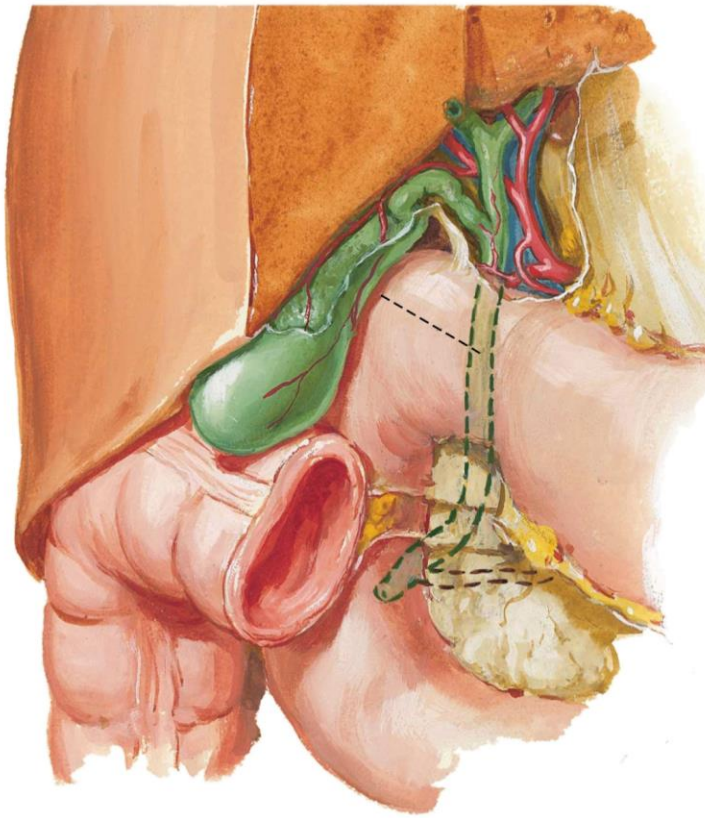
PERIHILAR - OUTCOMES

- 90-day mortality 10% (mostly liver failure) in two nation-wide series.[1,2] With ALPSS 40%.[3]
- Risk score for 90-day mortality: preop cholangitis, FLR<30%, PV reconstruction, incomplete FLR drainage.
- Median RFS 26 months; recurrence plateau at 8 years.[4]
- Only 18% initial isolated local recurrence.[4]
- Median OS 38 months after resection in Western series.
- Liver transplant: median OS 60 months (65% PSC)
- RF: N1, R1, poor tumor differentiation
- Only N1 precludes survival beyond 7 years.
- Several prognostic models that outperform AJCC.[5]

[1]Nuzzo, Arch Surg 2012;147:26
[2]Farges, BJS 2013;100:274
[3]Serenari, HPB 2016;18:419
[4]Groot Koerkamp, JACS 2015;221(6):1041
[5]Groot Koerkamp, Ann Onc 2015;26(9):1930

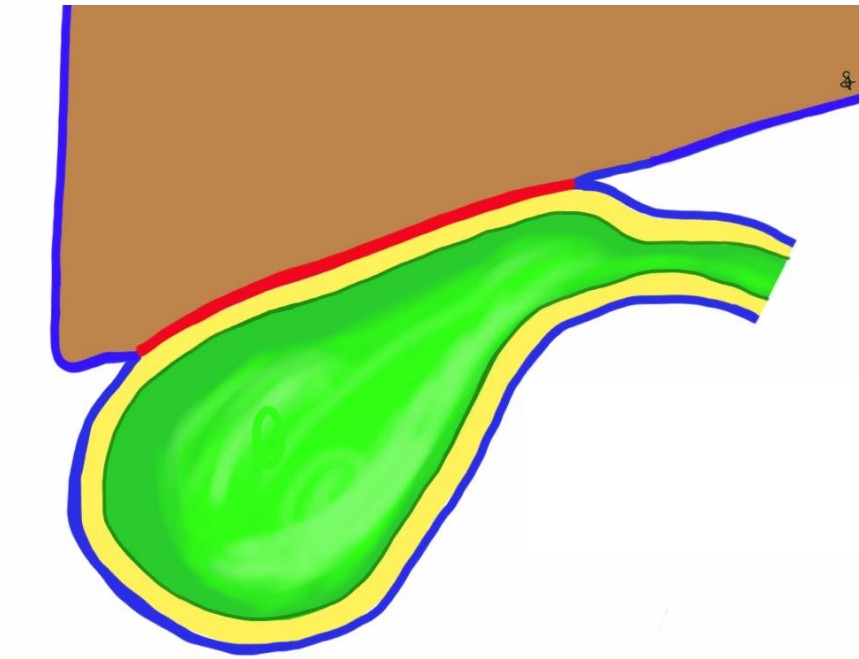
GALLBLADDER CA - PRESENTATION

- Incidence 3 in 100,000; 15,000 in EU
- Higher in Chili, Northern India
- RF: chronic inflammation, stones (90%)
- 2/3 incidental: at path exam after lap chole for stones
- 1/3 symptomatic: presenting with RUQ pain, weight loss, and mass on CT
- 40% of symptomatic patients are jaundiced (Chilean perihilar)
- 60% in fundus, 30% body, 10% neck



GALLBLADDER CA - STAGING

- Diagnostic work-up: CT chest-abdomen-pelvis
- GB facing liver has no peritoneum
- lap chole dissection between muscularis and cystic plate: R1 unless T1a
- Incidental: find out whether GB perforation, site of tumor, T-stage, cystic duct margin
- DD: Xanthogranulomatous cholecystitis up to 16%



GALLBLADDER CA - STAGING

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor invades lamina propria or muscular layer (Figure 20.3)
T1a	Tumor invades lamina propria
T1b	Tumor invades muscular layer
T2	Tumor invades perimuscular connective tissue; no extension beyond serosa or into liver (Figure 20.4)
T3	Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum, or extra-hepatic bile ducts
T4	Tumor invades main portal vein or hepatic artery or invades two or more extrahepatic organs or structures

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastases to nodes along the cystic duct, common bile duct, hepatic artery, and/or portal vein
N2	Metastases to periaortic, pericaval, superior mesenteric artery, and/or celiac artery lymph nodes

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T1-3	N1	M0
Stage IVA	T4	N0-1	M0
Stage IVB	Any T	N2	M0
	Any T	Any N	M1

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GALLBLADDER CA - INCIDENTAL

T-stage	Number of patients	Percentage of all stages (%)	Residual disease - (%)
T1	8	8	38
T2	67	68	57
T3	22	22	77
All stages	97	100	59

- MSK, 1998-2009
- n=135 re-exploration
- 61% recurrent disease
- No recurrent disease: median DFS 8 years, 10-year OS 60%
- Recurrent disease: median DFS 1 year, 10-year OS 15%

→ benefit of resection appears small

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Pawlik, JGS 2007;11(11)1478
Butte, JACS 2014;219(3):416

GALLBLADDER CA - RESECTION

- Staging laparoscopy for peritoneal or intrahepatic mets.
- Consider sampling aortocaval or celiac nodes (N2, stage IV).
- 2-3 cm wedge resection of segment IVb and V en-bloc with gallbladder with lymphadenectomy of the hepatoduodenal ligament.
- En-bloc resection of colon or duodenum if adherent to tumor: 50% has tumor involvement at final path (T3, stage III).
- Extrahepatic bile duct resection if cystic duct margin involved.

GALLBLADDER CA – DON'T...

- Don't resect patients with M1 or N2 disease.
- Don't resect patients with HA or PV involvement (T4, stage 4).
- Don't resect patients with GBC presenting with jaundice: no survivors beyond 2 years.[1]
- Don't perform a routine extrahepatic bile duct resection to clear possible microscopic disease.[2]
- Don't perform an extended liver resection for (occult) satellites or intrahepatic mets.
- Don't perform an extended lymphadenectomy.
- Don't perform port-sites resections for incidental GBC: disfiguring without survival benefit.

[1]Hawkins, Ann Surg Onc 2004;11(3):310
[2]Wiggers, HPB 2013

GALLBLADDER CA - OUTCOMES

- Postoperative mortality 1%
- Median OS without treatment: 5 months
- Only 16% complete resection (SEER)
- Median DFS: 1 year
- 85% of initial recurrence is distant (peritoneum, liver, lung)
- RF for recurrence: N1, R1, moderate/poor differentiation
- Other poor prognostic factors: bile spillage, jaundice, T2 on hepatic side (vs peritoneal side)
- Only 1 prognostic model for benefit adjuvant (chemo)rad.

Wang, JCO 2011;29(35):4627
http://skynet.ohsu.edu/nomograms/

SYSTEMIC TREATMENT

- ABC-02: the only phase 3 RCT for biliary tumors
- ICC, PHC, GBC, or ampullary cancer
- locally advanced/metastatic/recurrent
- n=420, mostly WHO 0/1
- gemcitabine +/- cisplatin
- Superior median OS in gem-cis group: 12 vs 8 months.
- Similar HR for all (extent of) disease subgroups
- Challenge: get patients requiring biliary drainage and recurring cholangitis to chemotherapy
- No RCT in adjuvant setting: ACTICCA is recruiting

Valle, NEJM 2010;362:14

IPNB

- Intraductal papillary neoplasm of the bile duct
- Intraductal growth (vs nodular-sclerosing)
- Precursor is exophytic (vs flat biliary dysplasia)
- 2010 – first appearance in WHO classification
- intrahepatic, perihilar, or distal
- 10% of bile duct tumors
- 75% invasive component at resection
- Diagnostic work-up and treatment as cholangiocarcinoma

Rocha, Hepatology 2012;56:1352

GALLBLADDER POLYP

- 5% healthy adults has gallbladder polyp of wall thickening.
- If polyps <12mm: no GBC[1]
- If polyp >20mm: 59% GBC[2]
- Guidelines: resect polyp if >10mm
- Exception: PSC, resect if >5mm
- Staging: CT, consider EUS to determine invasiveness
- Treatment: cholecystectomy, or en-bloc liver resection if concern invasion
- Avoid gallbladder perforation (1/3 in lap chole)
- Follow-up <10mm: 3 large series no GBC

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[1]Kozuka, Cancer 1982;50(10):2226
[2]Konstantinidis, JGS 2012;16(3):549

TAKE HOME MESSAGES

- Scrutinise imaging before and after surgery.
- Know and anticipate biliary and vascular variants.
- A biopsy is rarely needed prior to surgery: imaging determines management, biopsy peritoneal seeding, brush false-negative.
- Perform a quick staging laparoscopy in all patients with biliary tumors.
- Criteria for resection: complete resection is feasible, likely to improve survival, and acceptable postoperative mortality.
- Biliary tumors should only be treated in a tertiary referral center. Don't do a perihilar cholangio as your first case.

SELECTED REVIEW'S

- Hilar cholangiocarcinoma: expert consensus statement. - HPB (Oxford). 2015 Aug;17(8):691
- Gallbladder cancer: expert consensus statement. - HPB (Oxford). 2015 Aug;17(8):681
- Intrahepatic cholangiocarcinoma: expert consensus statement. - HPB (Oxford). 2015 Aug;17(8):669
- Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. – J Hep 2014;60:1268
- Resection of perihilar cholangiocarcinoma. -Surg Clin N Am 2016; 96:247
- Outcomes in biliary malignancy. - J Surg Oncol. 2014;110(5):585