

GALLBLADDER CANCER

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Agenda

- Case Presentation
- Epidemiology
- Pathogenesis & Pathology
- Staging
- Presentation & Diagnosis
- Stage-wise Management
- Outcomes/Prognosis
- Extra-hepatic Bile Duct Resection

Case Presentation

HPI

- ~~cc~~ 60 y.o. male
- Emesis postop after knee surgery
- Increased LFT
- Gallbladder mass on CT

PMH

- HTN, GERD, HLD, obesity
- Knee replacement
- Labs:
 - CBC: 5/12/39/319
 - BMP: wnl
 - AST/ALT: 236/169
 - Bili 0.4
 - Alk Phos 657

Procedure

- Exploratory Laparotomy
- Cholecystectomy
- Intraoperative cholangiogram
- Partial CBD resection with closure over t-tube
- Intraoperative ultrasound
- Liver biopsy
- Segments IV & V liver resection

Intraoperative course

- Frozen section:
gallbladder
adenocarcinoma with
positive cystic duct
margin
- EBL 1100ml
- IVF 4800ml
crystalloid
- T-tube, JP, NGT,
foley, CVC

Postoperative Course

- POD 1: admitted to SICU
- POD 4: decreased output from t-tube & increased bilious drainage from JP
- POD 5: Abd US – fluid collection in gallbladder fossa
- POD 6: T-tube cholangiogram – dislodged
- POD 10: ERCP w stent placement



Gallbladder Cancer

Epidemiology

- In 2010: 9,760 new cases & 3,320 deaths in US
- 2-6 times more common in women than men
- Northern Indian & Meso-Americans (gallstones), Asians (Anomalous Pancreatico-Biliary Duct Junction)



Pathogenesis

Gallstones

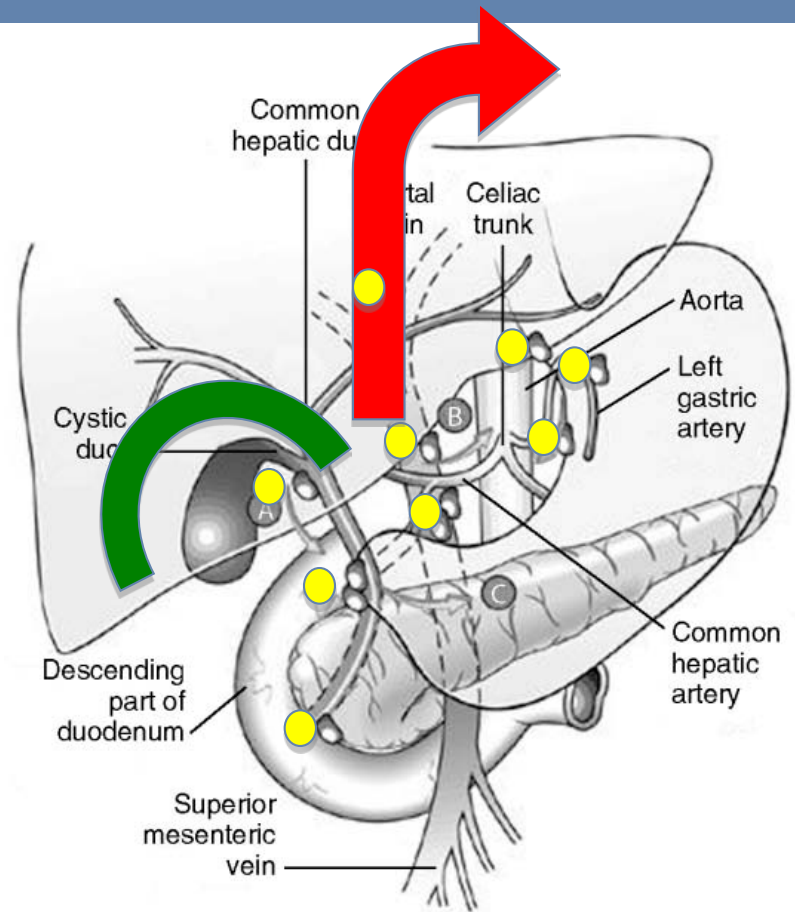
- Chronic irritation of gallbladder mucosa and ducts by changes in inorganic composition of bile
- Progression from dysplasia → carcinoma
- p53 mutation

APBDJ

- proximal pancreatic-CBD junction predisposes to reflux of pancreatic secretions into bile ducts
- epithelial hyperplasia → papillary tumors
- K-ras mutation

Pathology

- 80% adenocarcinoma
- Morphology:
 - ▣ Infiltrative or nodular
 - ▣ papillary (best prognosis)
- Routes of invasion
 - ▣ Direct extension (liver, duodenum, colon, ducts)
 - ▣ Lymphatics
 - ▣ Hematogenous (lung, brain)
 - ▣ Peritoneal seeding



TNM classification

- Tis: carcinoma in situ
- T1: invades lamina propria and/or muscularis
- T2: invades perimuscular connective tissue but not beyond serosa or into liver
- T3: invades through serosa or directly invades liver or other adjacent organ

Staging

artery

| Stage 0 | Tis | N0 | M0 |
|-----------|-------|------|----|
| Stage IA | T1 | N0 | M0 |
| Stage IB | T2 | N0 | M0 |
| Stage IIA | T3 | N0 | M0 |
| Stage IIB | T1-3 | N1 | M0 |
| Stage III | T4 | N0-1 | M0 |
| Stage IV | Any T | N0-1 | M1 |

Diagnosis

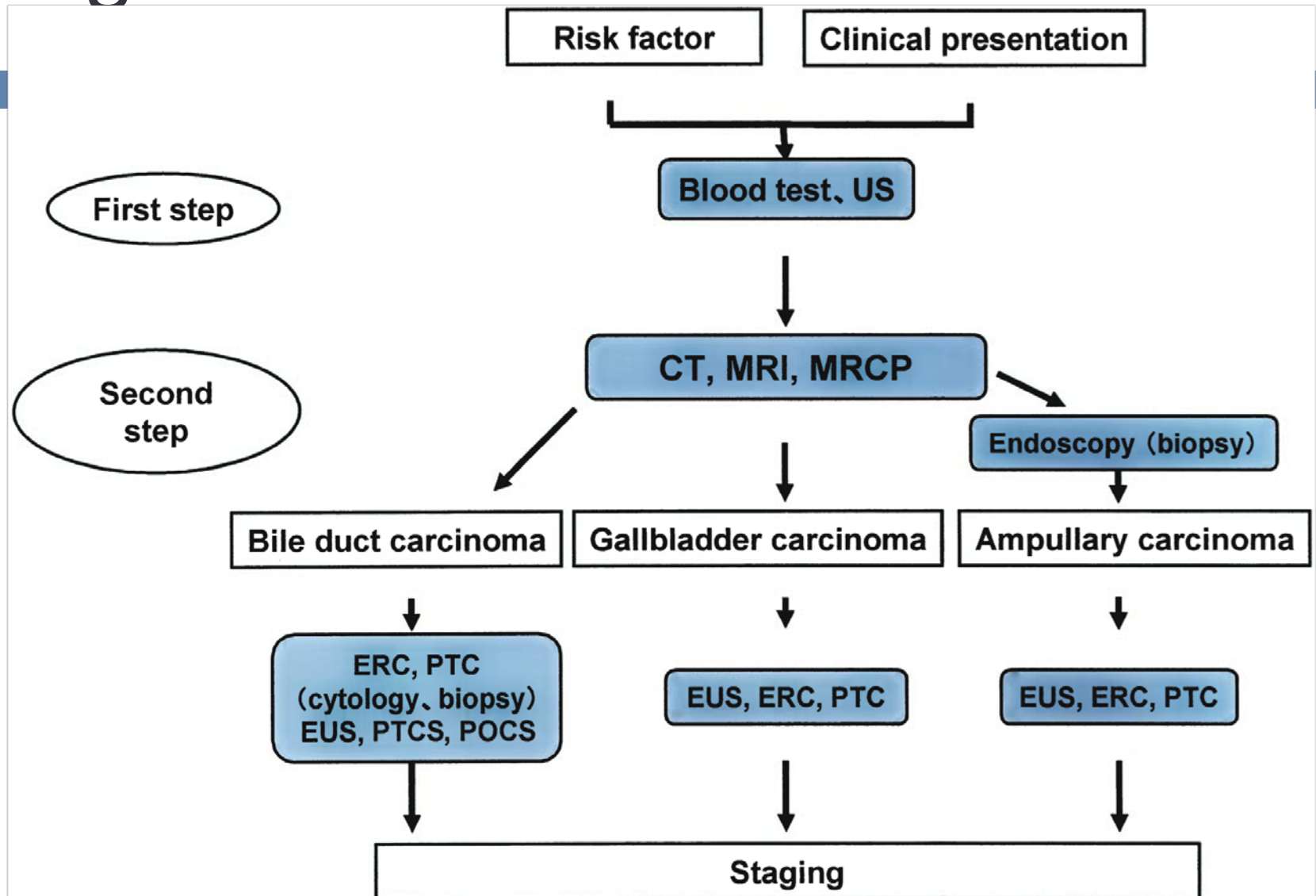
Risk Factors

- Cholelithiasis (0.5-3%)
- Porcelain Gallbladder (12-60%)
- APBDJ: Anomalous Pancreatico-Biliary Duct Junction (38-93%)
- Infection (salmonella)
- Carcinogens (radon, nitrosamines)

Presentation

- Most common symptom RUQ pain (75%)
- Jaundice (45%), fever, nausea, vomiting, weight loss, anorexia, abdominal distension
- Incidentally s/p cholecystectomy

Diagnosis



Diagnosis

First Step: Labs + AUS

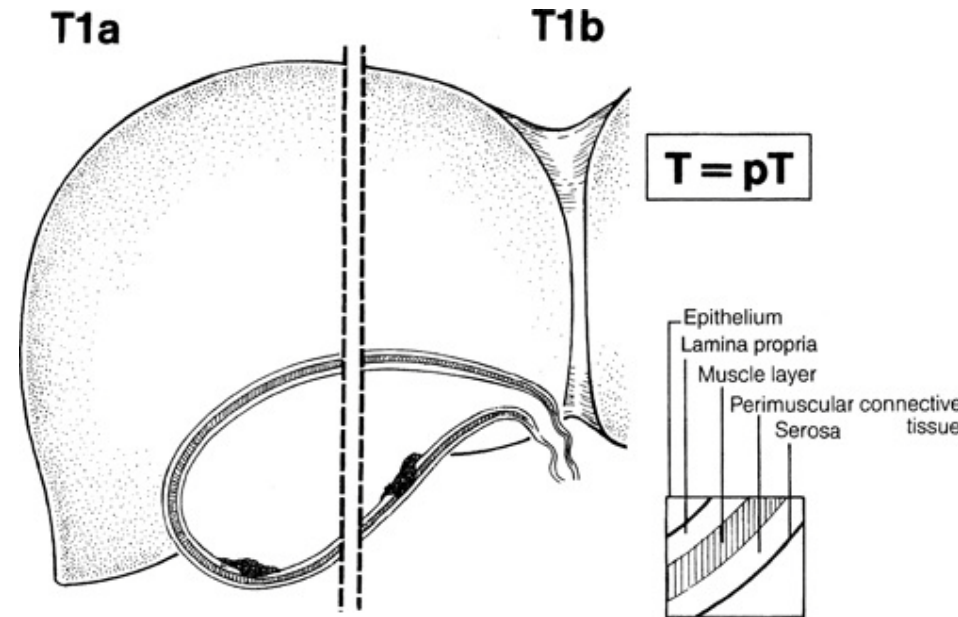
- CA 19-9: 50-79%
- CEA: 40-70%
- Ultrasound 50% sensitive
 - ▣ Mural thickening or calcification
 - ▣ Gallbladder mass
 - ▣ Loss of gallbladder wall-liver interface

Second Step: extent of tumor

- EUS: sensitivity 92-97%
- CT: sensitivity 88%, specificity 87%, accuracy of Dx resectability 93%
- MRI/MRCP:
 - ▣ Invasion into liver: 67-100% sensitivity, 89% specificity
 - ▣ Invasion into bile duct: 62-100% sensitivity, 89% specificity
 - ▣ Lymph node mets: 56-92% sensitivity, 89% sensitivity

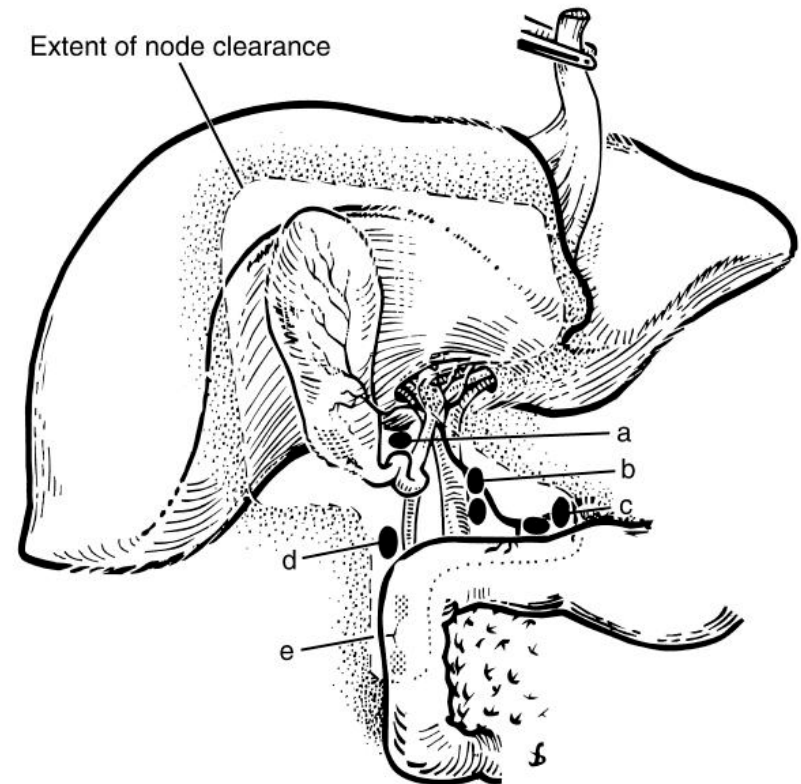
Management: Stages 0 and IA

- Tis & T1 tumors
- Often incidentally found on pathologic examination of cholecystectomy specimen
- Simple cholecystectomy is sufficient. Port site excision recommended



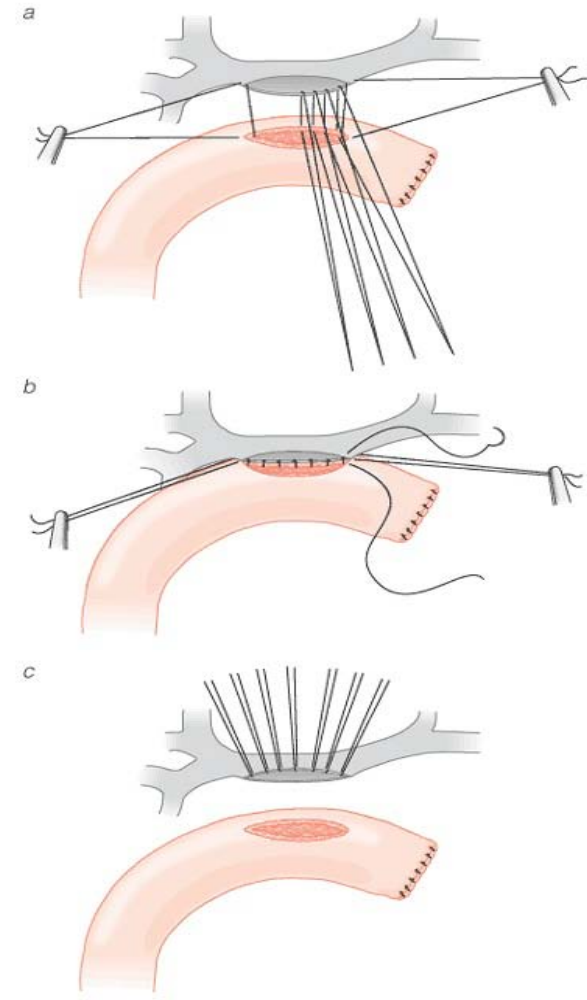
Management: Stage IB

- T2 tumors
- R0 resection: 2cm margins
- Radical Cholecystectomy:
 - Cholecystectomy
 - Cystic duct excision
 - Segments IV & V resection vs. 2cm adjacent liver
 - Regional lymphadenectomy:



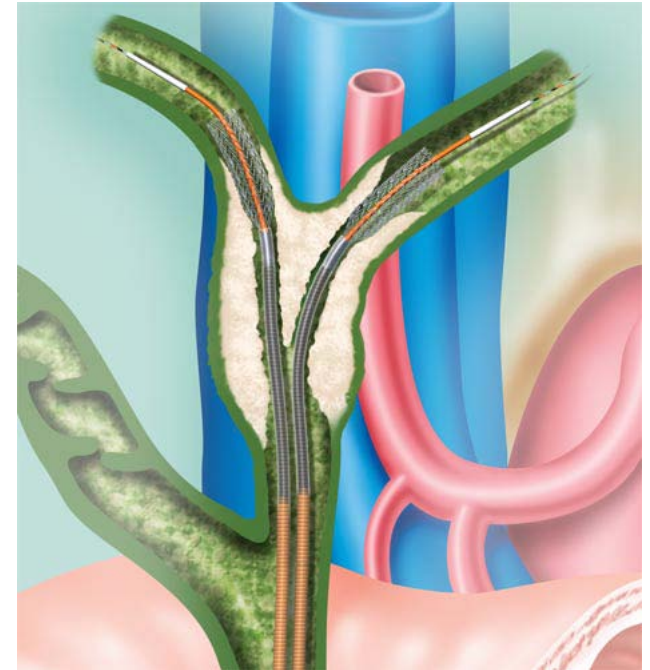
Management: Stage IIA

- T3 tumors
- Radical cholecystectomy with en-bloc resection of involved organs in selected patients
- After routine cholecystectomy if cystic duct margin positive: Re-exploration and radical cholecystectomy with CBD excision, regional lymphadenectomy, and hepaticojejunostomy is indicated
- Perioperative mortality 18%



Management: Stage IIB - IV

- T4, any nodes, or distant mets
- unresectable
- Endoscopically or radiologic stent placement
- Palliative surgery for severe symptoms of duct obstruction (pruritis, hepatic dysfunction, cholangitis)
- Clinical trial enrollement – standard chemotherapy not effective



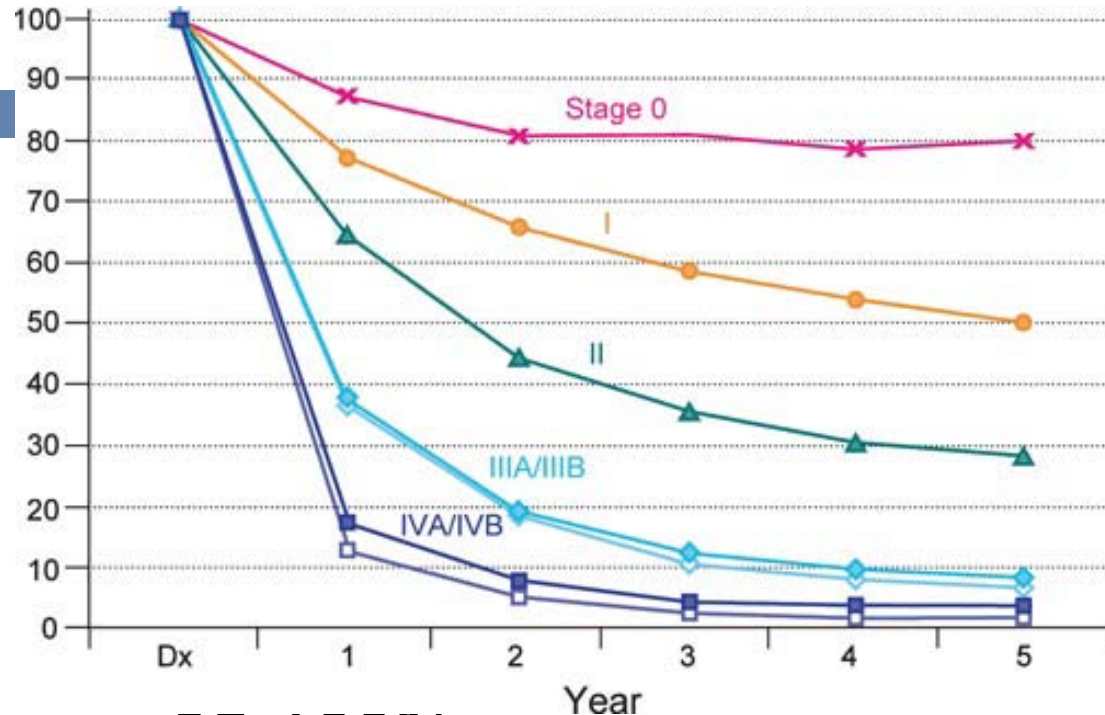
Outcomes

Stage at Diagnosis

- Stage 0-IA: 25%
- Stage IB-III: 35%
- Stage IV: 40%

5-year survival

- Overall: <5%
- T1 → cholecystectomy: 85-100%
- T2 → cholecystectomy: 25%
 - extended cholecystectomy + lymphadenectomy: 70%
- T3 → R0 resection: 20-50%
- T4: median survival 1-3 months



Gallbladder Cancer Involving the Extrahepatic Bile Duct is Worthy of Resection.

Nishio, Hideki; Ebata, Tomoki; Yokoyama, Yukihiro; Igami, Tsuyoshi; Sugawara, Gen; Nagino, Masato

Annals of Surgery. 253(5):953-960, May 2011.

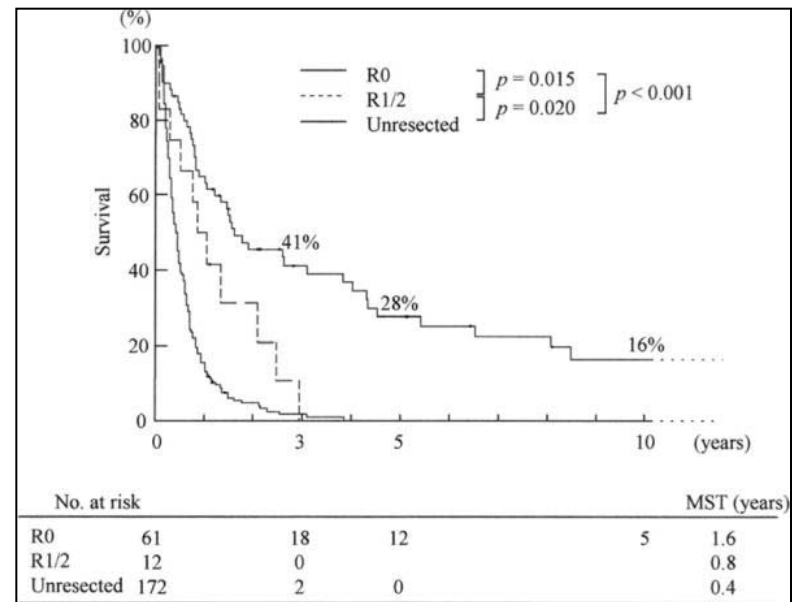
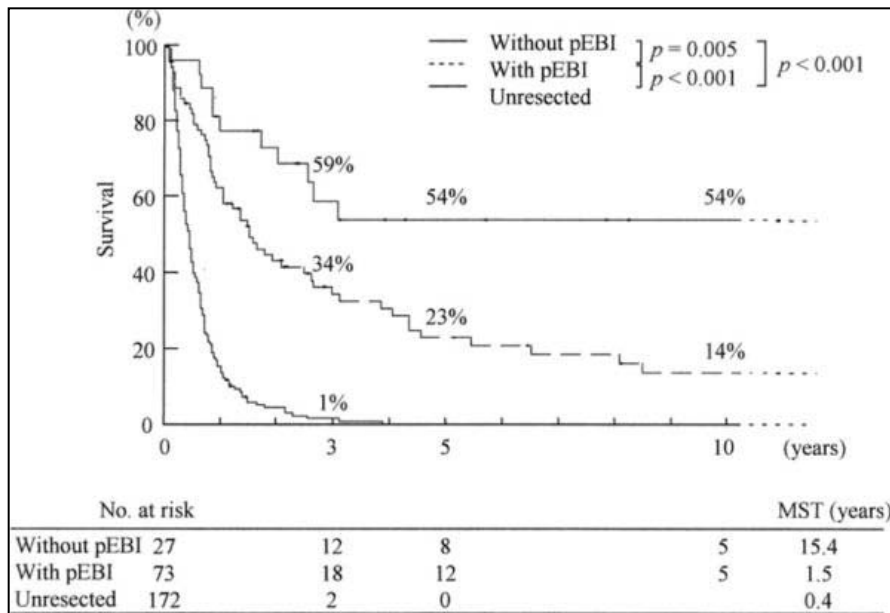
DOI: 10.1097/SLA.0b013e318216f5f3

- Retrospective review of 436 patient case series with gallbladder cancer
- 100 patients with biliary invasion (T3 or T4)

Extrahepatic Bile Duct Involvement

Independent predictor of poor outcome compared to other T3 disease

Survival benefit seen if R0 resection can be performed



Systematic Review: Should Routine Resection of the Extrahepatic Bile Duct Be Performed in Gallbladder Cancer?

Parul J. Shukla, Savio G. Barreto¹

- Concept of field cancerization: entire biliary tree is at risk for developing malignancy due to exposure to carcinogenic process or substance
- Aids in complete lymphadenectomy
- Extrahepatic bile duct resection included as part of radical resection for all stages of gallbladder cancer by Japanese surgeons
- Can a survival benefit be shown?

Table 1: Levels of evidence of studies supporting routine EHBD resection for gallbladder cancer

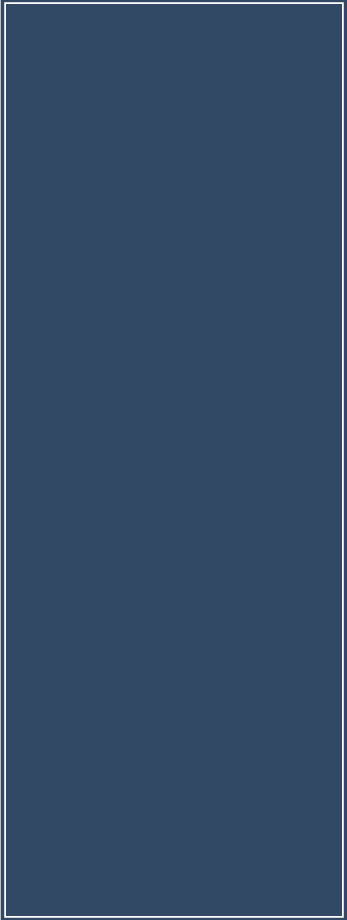
| Author (Ref) | No. of patients | Conclusions | Level of evidence ^[29] |
|--|---------------------------|--|-----------------------------------|
| Studies supporting routine EHBD excision in T2 disease | | | |
| Suzuki <i>et al.</i> ^[30] | 20 (T2 disease) | 5YSR - 77% | IV - V |
| | 8 / 20 - no EHBD excision | 5YSR - 100% | |
| Shimada <i>et al.</i> ^[31] | 41 | 3YSR | IV - V |
| | T1 - 4 | 100% | |
| | T2 - 21 | 74.8% | |
| | T3/4 - 16 | 6.7% | |
| Nagakura <i>et al.</i> ^[32] | 63 | Poor survival in patients with overt and micrometastases to nodes | IV - V |
| Shirai <i>et al.</i> ^[34] | 48 | 5YSR - 90% | IV - V |
| Wise <i>et al.</i> ^[36] | 5 | 100% disease free at follow-up ranging from 15 to 83 months | V |
| Chijiwa <i>et al.</i> ^[37] | 52 | 5YSR | IV - V |
| | | T1 - 100% | |
| | | T2 - 60.8% | |
| | | T3/4 - 0% | |
| Studies supporting routine EHBD excision in T3/4 disease | | | |
| Todoroki <i>et al.</i> ^[9] | 135 | 5YSR | IV - V |
| | T1 - 13 | 100% | |
| | T2 - 24 | 70% | |
| | T3 - 9 | 19% | |
| | T4 - 89 | 5% | |
| Kosuge <i>et al.</i> ^[38] | 55 | No difference in survival with or without EHBD excision in stages 1-3 but only for stage 4 | IV |
| Kaneoka <i>et al.</i> ^[39] | 59 | Benefit of bile duct resection is restricted to patients without bile duct invasion | IV - V |

Table 2: Stage-wise distribution of studies highlighting the lack of benefit of routine EHBD resection for gallbladder cancer

| Study | Stage | Effect on survival | Complication |
|---|------------------|--|------------------------------|
| Chijiwa <i>et al.</i> , 2001 ^[11] | T2 N0-2 | None | Anastomotic leak |
| Pawlik <i>et al.</i> , 2007 ^[41] | n=42; T2 | None; no effect on number of lymph nodes harvested | Not specifically addressed |
| Shimada <i>et al.</i> , 1997 ^[31] | T3/4 | None | Anastomotic leak |
| Bartlett <i>et al.</i> , 1996 ^[44] | n=10; all stages | Not specifically addressed | 50% |
| Kokudo <i>et al.</i> , 2003 ^[40] | n=33; all stages | None | Not specifically addressed |
| Muratore <i>et al.</i> , 2000 ^[42] | n=33; all stages | None | High morbidity and mortality |
| Behari <i>et al.</i> ^[43] | n=10; all stages | None | Bile leak |

*CHD — common hepatic duct

Indications for EHBD Resection

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- Tumors involving EHBD
 - Lymph node enlargement close to CBD
 - Positive cystic duct margin on intraoperative frozen section
 - APBDJ (risk for metachronous lesions)
 - Re-resection (lymph node dissection difficult due to fibrosis)

Thank You!

References

- ❑ AJCC Cancer Staging Handbook, 7th Ed (2010)
- ❑ Cameron “Current Surgical Therapy” 6th ed
- ❑ Maingot’s Abdominal Operations
- ❑ Miyakawa S, et al. “Flowcharts for the management of biliary tract and ampullary carcinomas” J Hepatobiliary Pancreat Surg (2008) 15:7-14.
- ❑ National Cancer Institute Gallbladder Cancer Treatment PDQ 7/20/2010
- ❑ Nishio H et al. “Gallbladder cancer involving the extrahepatic bile duct is worthy of resection” Ann Surg (2011) 253: 953-60.
- ❑ Schwartz’s Principles of Surgery, 9th ed
- ❑ Shukla PJ & Barreto SG. “Systematic Review: Should routine resection of the extra-hepatic bile duct be performed in gallbladder cancer?” Saud J Gastroenterol (2010) 16: 161-7