GALLBLADDER CANCER

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Downstate Surgery M&M
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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

- xx yo patient
- 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
Exploratory Laparotomy

Cholecystectomy

Intraoperative cholangiogram

Partial CBD resection with closure over t-tube

Intraoperative ultrasound

Liver biopsy

Segments IV & V liver resection

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

<table>
<thead>
<tr>
<th>Gallstones</th>
<th>APBDJ</th>
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</thead>
<tbody>
<tr>
<td>- Chronic irritation of gallbladder mucosa and ducts by changes in inorganic composition of bile</td>
<td>- proximal pancreatic-CBD junction predisposes to reflux of pancreatic secretions into bile ducts</td>
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<tr>
<td>- Progression from dysplasia → carcinoma</td>
<td>- epithelial hyperplasia → papillary tumors</td>
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<tr>
<td>- p53 mutation</td>
<td>- K-ras mutation</td>
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</table>
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
- **T4**: invades portal vein or hepatic artery

**Staging**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tis</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IA</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T1-3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T4</td>
<td>N0-1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>N0-1</td>
<td>M1</td>
</tr>
</tbody>
</table>
# 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

First step

Second step

Risk factor

Clinical presentation

Blood test, US

CT, MRI, MRCP

Endoscopy (biopsy)

Bile duct carcinoma

Gallbladder carcinoma

Ampullary carcinoma

ERC, PTC (cytology, biopsy)
EUS, PTCS, POCS

EUS, ERC, PTC

EUS, ERC, PTC

Staging
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

www.downstatesurgery.org
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: Extent of node clearance

www.downstatesurgery.org
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%

www.downstatesurgery.org
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%

Overall 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

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?

¹ Downstate Surgery Website: www.downstatesurgery.org
<table>
<thead>
<tr>
<th>Author (Ref)</th>
<th>No. of patients</th>
<th>Conclusions</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Suzuki et al.</strong>[^30]</td>
<td>20 (T2 disease)</td>
<td>5 YSR - 77%</td>
<td>IV - V</td>
</tr>
<tr>
<td>Shimada et al.[^31]</td>
<td>8 / 20 - no EHBD excision</td>
<td>5 YSR - 100%</td>
<td>IV - V</td>
</tr>
<tr>
<td></td>
<td>41</td>
<td>3 YSR</td>
<td>IV - V</td>
</tr>
<tr>
<td></td>
<td>T1 - 4</td>
<td>100%</td>
<td>IV - V</td>
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<tr>
<td></td>
<td><strong>T2 - 21</strong></td>
<td><strong>74.8%</strong></td>
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<td></td>
<td>T3/4 - 16</td>
<td>6.7%</td>
<td></td>
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<tr>
<td>Nagakura et al.[^32]</td>
<td>63</td>
<td>Poor survival in patients with overt and micrometastases to nodes</td>
<td>IV - V</td>
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<tr>
<td>Shirai et al.[^34]</td>
<td>48</td>
<td>5 YSR - 90%</td>
<td>IV - V</td>
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<tr>
<td>Wise et al.[^36]</td>
<td>5</td>
<td>100% disease free at follow-up ranging from 15 to 83 months</td>
<td>V</td>
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<tr>
<td>Chijiwa et al.[^37]</td>
<td>52</td>
<td>5 YSR</td>
<td>IV - V</td>
</tr>
<tr>
<td></td>
<td>T1 - 100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>T2 - 60.8%</strong></td>
<td></td>
<td></td>
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<tr>
<td>Todoroki et al.[^9]</td>
<td>135</td>
<td>5 YSR</td>
<td>IV - V</td>
</tr>
<tr>
<td></td>
<td>T1 - 13</td>
<td>100%</td>
<td></td>
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<td></td>
<td>T2 - 24</td>
<td>70%</td>
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<td></td>
<td>T3 - 9</td>
<td>19%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T4 - 89</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Kosuge et al.[^38]</td>
<td>55</td>
<td>No difference in survival with or without EHBD excision in stages 1-3 but only for stage 4</td>
<td>IV</td>
</tr>
<tr>
<td>Kaneoka et al.[^39]</td>
<td>59</td>
<td>Benefit of bile duct resection is restricted to patients without bile duct invasion</td>
<td>IV - V</td>
</tr>
<tr>
<td>Study</td>
<td>Stage</td>
<td>Effect on survival</td>
<td>Complication</td>
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<tr>
<td>------------------------------</td>
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<td>---------------------------------------------------------</td>
<td>-----------------------------------</td>
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<tr>
<td>Pawlik et al., 2007[41]</td>
<td>n=42; T2</td>
<td>None; no effect on number of lymph nodes harvested</td>
<td>Not specifically addressed</td>
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<tr>
<td>Shimada et al., 1997[31]</td>
<td>T3/4</td>
<td>None</td>
<td>Anastomotic leak</td>
</tr>
<tr>
<td>Bartlett et al., 1996[44]</td>
<td>n=10; all stages</td>
<td>Not specifically addressed</td>
<td>50%</td>
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<tr>
<td>Kokudo et al., 2003[40]</td>
<td>n=33; all stages</td>
<td>None</td>
<td>Not specifically addressed</td>
</tr>
<tr>
<td>Muratore et al., 2000[42]</td>
<td>n=33; all stages</td>
<td>None</td>
<td>High morbidity and mortality</td>
</tr>
<tr>
<td>Behari et al.[43]</td>
<td>n=10; all stages</td>
<td>None</td>
<td>Bile leak</td>
</tr>
</tbody>
</table>

*CHD — common hepatic duct
Indications for EHBD Resection

- 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

- Cameron “Current Surgical Therapy” 6th ed
- Maingot’s Abdominal Operations
- National Cancer Institute Gallbladder Cancer Treatment PDQ 7/20/2010
- Schwartz’s Principles of Surgery, 9th ed