DDW 2016
Pancreatobiliary point of view

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GIDRC
IUMS
Management of Biliary strictures

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Center for Endoscopy and Pancreatobiliary Disorders

Cleveland Clinic
Outline

- Resectable malignant strictures
  Preoperative Biliary drainage or not?
- Palliation of unresectable hilar strictures
  Unilateral or Bilateral Stenting?
- Dominant strictures in PSC
  Stent or just Dilate?
Outline

- Resectable malignant strictures
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  Stent or just Dilate?
Preoperative drainage: Rationale

• Cholestasis is associated with higher post-op morbidity and mortality
• Preoperative drainage may improve outcome by:
  – Improving liver synthetic function
  – Increase clearance of endotoxins
  – Improve GI mucosal barrier function (reduce bacterial translocation)

Do the benefits outweigh the risks?

Resolved Jaundice
Improved liver function

Stent dysfunction
Infections
Seeding (PTHC)
RCT in Pancreatic Head Cancer

- Obstructive Jaundice
  - Bilirubin 2.3-14.6 mg/dl
  - PBD Group
    - ERCP + plastic stent
      - Surgery
        - After 4-6 weeks
      - Surgery within 1 week
      - Serious Complications within 120 days
  - Early surgery Group

van der Gaag et al. NEJM 2010;362:129-37
# Study Findings

<table>
<thead>
<tr>
<th></th>
<th>PBD</th>
<th>Early Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>N = 102</td>
<td>N = 94</td>
</tr>
<tr>
<td>Surgery related complications</td>
<td>47%</td>
<td>37%</td>
</tr>
<tr>
<td>Serious complications</td>
<td>74%</td>
<td>39%</td>
</tr>
<tr>
<td>Mortality</td>
<td>9%</td>
<td>4%</td>
</tr>
</tbody>
</table>

PBD with stent placement has no beneficial effect on surgical outcome

van der Gaag et al. NEJM 2010;362:129-37
Critiques

- Exclusion of severe jaundice (Bilirubin > 14.6)
- Higher than expected rate of ERCP-related complications (46%)
- If they had used metallic stents
  - Stent-related complications would have been lower
  - Results might have been different
RCT in Pancreatic Head Cancer

early surgery not possible logistical issues

ERCP + Metal stent
Surgery After 4-6 weeks

ERCP + plastic stent
Surgery After 4-6 weeks

Obstructive Jaundice Bilirubin 2.3-14.6 mg/dl

Surgery within 1 week

Serious Complications within 120 days

Tol et al. Gut; in Press
## Complications: Plastic vs. Metal

<table>
<thead>
<tr>
<th></th>
<th>Plastic Stent</th>
<th>Metal Stent</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients #</td>
<td>N=102</td>
<td>N=49</td>
<td></td>
</tr>
<tr>
<td>PBD related complications</td>
<td>46%</td>
<td>24%</td>
<td>P=0.011</td>
</tr>
<tr>
<td>Stent related (occlusion, exchange)</td>
<td>30%</td>
<td>6%</td>
<td>P=0.003</td>
</tr>
</tbody>
</table>

Tol et al. Gut; in Press
Complications: PBD vs. Early Surgery

<table>
<thead>
<tr>
<th></th>
<th>Plastic Stent</th>
<th>Metal Stent</th>
<th>Early Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Complications (endoscopic, surgical)</td>
<td>74%</td>
<td>51%</td>
<td>39%</td>
</tr>
</tbody>
</table>

Early Surgery still preferable to PBD independent of stent type

Tol et al. Gut; in Press
Meta-analysis of RCTs

PBD in Distal Strictures

- 4 RCT using PTHC, 2 RCT using ERCP drainage
- 520 patients (PBD 265, No PBD 255)
- No difference in Mortality
- No difference in hospital length of stay
- PBD pts. had higher morbidity

Recommendations
PBD for Resectable Distal Strictures

• Not routinely
• Operative candidate: Early surgery

PBD indicated in:
  – Cholangitis
  – Severely symptomatic (itching)
  – Delayed surgery (logistics)
  – Need for neoadjuvant therapy

• If Drainage → use metal stent (covered, if uncovered shortest possible to prevent interference with surgery)

### PBD in Hilar strictures

<table>
<thead>
<tr>
<th>Year (1st Author)</th>
<th>Design</th>
<th>N Total (PBD)</th>
<th>Study Findings Effect of PBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999 (Hochwald)</td>
<td>Retrospective</td>
<td>71 (42)</td>
<td>Increased post-op infections</td>
</tr>
<tr>
<td>2000 (Figueras)</td>
<td>Retrospective</td>
<td>20 (11)</td>
<td>No effect on mortality or morbidity, increased length of hospital stay</td>
</tr>
<tr>
<td>2009 (Ferrero)</td>
<td>Retrospective</td>
<td>60 (30)</td>
<td>No effect on mortality, increased post-op infections</td>
</tr>
<tr>
<td>2010 (Grandonadam)</td>
<td>Retrospective</td>
<td>38 (15)</td>
<td>No effect on 5-year survival, decreased incidence of intra-abd. abscess</td>
</tr>
<tr>
<td>2013 (Farges)</td>
<td>Retrospective</td>
<td>366 (180)</td>
<td>No effect on post-op. mortality</td>
</tr>
</tbody>
</table>

References:
- Arch Surg 1999;134: 261-66
- Liver Transpl 2000;6: 786-94
- Am Surg Oncol 2010;17: 3155-61
- Br J Surg 2013;100:274-83

There is no RCT
Current Recommendations
PBD in Malignant Hilar Strictures

• Not routinely
• PBD indicated in pts with:
  – Cholangitis
  – Need for neo-adjuvant therapy
  – Hyperbilirubinemia-induced malnutrition, hepatic insuff, renal insuff

American HPB Association consensus statement  HPB 2015; 17: 691-99
Outline

- Resectable malignant strictures
  Pre-operative biliary drainage?

- Palliation of unresectable hilar strictures
  Unilateral or Bilateral Stenting?

- Dominant strictures in PSC
  Stent or just dilate?
Malignant Hilar Strictures

- Regardless of histology <30% are suitable for curative resection
- Palliation needed for majority of patients
- Biliary drainage major component of palliation
There are just Two RCTs in this regard

<table>
<thead>
<tr>
<th></th>
<th>Unilateral</th>
<th>Bilateral</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>79</td>
<td>78</td>
</tr>
<tr>
<td>Technical Success</td>
<td>87%</td>
<td>77%</td>
</tr>
<tr>
<td>Complications</td>
<td>19%</td>
<td>27%</td>
</tr>
<tr>
<td>(Cholangitis)</td>
<td>(8.8%)</td>
<td>(16.6%)</td>
</tr>
<tr>
<td>Drainage Success</td>
<td>81%</td>
<td>73%</td>
</tr>
<tr>
<td>(75% ↓ Bilirubin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival</td>
<td>4.7 m</td>
<td>4.7 m</td>
</tr>
</tbody>
</table>

**Study conclusion** → **Routine bilateral stenting not advised**

De Palma et al. GIE 2001;53:547-53
• **Unilateral vs. bilateral (independent of stent type):**
  - No difference in patency time (uni vs bilat)
  - Reintervention success 100% (uni) vs 68% (bilat)
    
    P = 0.02
  - SEMS: Longer patency, less reintervention

## Other Studies

<table>
<thead>
<tr>
<th>Year</th>
<th>(1&lt;sup&gt;st&lt;/sup&gt; Author)</th>
<th>Design</th>
<th>N Total (Unilat.)</th>
<th>Study Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>Chang</td>
<td>Retrospective Plastic stent</td>
<td>118 (69)</td>
<td>Survival worst if both lobes injected and only one drained</td>
</tr>
<tr>
<td>2003</td>
<td>Freeman</td>
<td>Prospective SEMS</td>
<td>35 (31)</td>
<td>Unilat stenting adequate (only 4 has bilat stent)</td>
</tr>
<tr>
<td>2009</td>
<td>Naitoh</td>
<td>Retrospective SEMS</td>
<td>46 (17)</td>
<td>Bilat stenting → longer patency Same survival and complications</td>
</tr>
<tr>
<td>2010</td>
<td>Iwano</td>
<td>Retrospective SEMS</td>
<td>82 (65)</td>
<td>Unilateral stenting → Lower infect. Same survival and stent patency</td>
</tr>
<tr>
<td>2012</td>
<td>Liberato</td>
<td>Retrospective SEMS / Plastic</td>
<td>136 (56)</td>
<td>Bilat. Stenting → longer patency Same survival Metal → longer patency than plastic</td>
</tr>
<tr>
<td>*2010</td>
<td>Vienne</td>
<td>Retrospective</td>
<td>106</td>
<td>&gt;50% drainage → longer survival Atrophic lobe stent ↑ complications</td>
</tr>
</tbody>
</table>

Chang *GIE* 1998; 47:354-62  
Naitoh. *J Gastro Hepat* 2009;24:552  
Most Recent Meta-Analysis
Unilateral vs. Bilateral Stenting

- 7 Studies
- 634 Patients
- No difference in mortality
- No difference in stent occlusion rate
- No difference in cholangitis rate

⇒ No benefit to bilateral stenting

Sawas et al. GIE 2015;82:256-267
Recommendations
Palliation of unresectable hilar strictures

- Imaging (CT, MRI) before palliative drainage
  - “Road map”; Avoid stenting of atrophic lobe
- Unilateral stenting adequate in most cases
- Bilateral injection of contrast needs bilateral drainage
- Metallic stents have longer patency and need less re-intervention than plastic stents
Outline

- Resectable malignant strictures
  Pre-operative biliary drainage or not?

- Palliation of hilar strictures
  Unilateral or Bilateral Stenting

- Dominant strictures in PSC
  Stent or just Dilate?
Primary Sclerosing Cholangitis

- Chronic progressive disease affecting intrahepatic and extrahepatic bile ducts

- Involvement:
  - Intrahepatic and extrahepatic: 69%
  - Intrahepatic only: 25%
  - Extrahepatic only: 4%

Chapman et al. AASLD guidelines. Hepatology 2010;51:660-78
Dominant Strictures

- 45% - 58% of patients
- In addition to CCA, associated with:
  - Cholangitis
  - Stone formation
  - Hepatic decompensation

→ Treatment

AASLD Practice Guidelines. Hepatology 2010;51:660-78
Endoscopy for dominant strictures

- Preferred mode of therapy
- Multiple observational studies:
  - Clinical improvement (↓pruritus, cholangitis)
  - Biochemical improvement (↓cholestasis)
  - Radiological improvement (↑diameter of duct)

Chapman et al. AASLD Practice Guidelines. Hepatology 2010;51:660-78
Optimal Endoscopic Approach

?  Balloon  Stent  Combination
There is No RCT in this regard

Balloon vs. Stenting
Retrospective Study

- 71 patients
- 34 balloon dilatation
- 37 Balloon dilatation + stenting (ERCP & PTHC)
- Compared adverse events
  - Median follow up: 24 months

Current Recommendations
Dominant strictures in PSC

• ERCP with balloon dilatation effective in most
• Routine stenting after dilatation of a dominant stricture is NOT recommended
• If stenting is performed, consider short term stenting (< 2 weeks)

Lindor et al. ACG clinical guidelines 2015; 110:646-59
Plugging holes: biliary and pancreatic duct leaks

- Occurs in conditions related to operative intervention, trauma, or inflammation
- Successful leak closure relies on eliminating or bypassing the transpapillary pressure gradient.
Biliary Leaks

- Defined by bile outside the biliary tree
- Post operative
  - Cholecystectomy (0.3-0.9% incidence)
  - Liver resection (as high as 24%)
  - Liver transplant (2-25%)
Recognition

- Clinical suspicion
- USG
  - Lap choley postoperative fluid collection in 20%
- HIDA (up to 100% sensitive and specific)$^1$
- CT/MRI - MRCP valuable for bile duct injury
- ERCP

Biliary Leaks-Therapy

- First consideration should be percutaneous drainage of fluid collection

- ERCP-Reduction of transpapillary pressure gradient
  - Sphincterotomy
  - Stent
    - Bypass leak site
      - T tube pulls
      - Common bile duct injury
Biliary Leaks-Therapy

- Sphincterotomy alone in the treatment of bile leaks.
  - 22/25 sealed after 6 weeks\(^2\) (12% failure rate)
  - 27/31 subjects sealed by 3 weeks\(^3\) (13% failure rate)

Hepatogastroenterology. 2002 Nov-Dec;49(48):1496-8
Biliary Leaks-Therapy

- Stent vs Stent and sphincterotomy
  - Randomized study comparing 7fr stent (n=24) vs sphx and 10fr stent (n=28)\(^4\)
  - The overall complication rate was 4.16\% for the first group and 10.71\% for the second (P=0.615). All leaks sealed up, but 2 of the 7 fr required a 10fr stent

Does stent size matter

- 10fr vs 7 fr
  - A comparative study of 10-Fr vs. 7-Fr straight plastic stents in the treatment of postcholecystectomy bile leak, 63 patients randomized (7fr 31, 10fr 32),
    - after 4 weeks 93% of 7 fr and 96% of 10 fr leaks healed, 27 fr'ers up sized to 10 fr after one week
  - But:
    - 10 fr stents may increase risk of post ERCP pancreatitis if placed without a sphx (not statistically significant)

How long

- Over 90% of uncomplicated leaks will heal in 4-6 weeks
- Repeat cholangiography demonstrated findings requiring intervention 22.7%
Defiant biliary leaks

- Options
  - Prolonged stenting with multiple plastic stents
  - Fully covered metal stents - not FDA approved for this indication
  - Case reports
Prevention of Post-ERCP Pancreatitis

B. Joseph Elmunzer
ASGE Clinical symposium
23 May 2016
Prevention of PEP

1) Appropriate patient selection
2) Risk stratification
3) Atraumatic/efficient procedural technique
4) Prophylactic pancreatic stent placement
5) Pharmacoprevention
Prophylactic pancreatic stent placement

- Preserves pancreatic duct drainage (orifice edema)
- 12 RCTs & >12 non-randomized studies – benefit
- RRR ~60%; ARR 10-15%
- NNT 8 (95% CI, 6-11)
- Profound reduction in severe/necrotizing pancreatitis

Choudhary et al. Gastrointest Endosc 2011
Mazaki et al. J Gastroenterol 2014
Pancreatic stents: disadvantages

- Dangerous if attempted but unsuccessful*
- Non-pancreatitis stent complications (4-5%)**
- Stent-related pancreatic duct changes
- Inconvenient & costly
  - Abdominal X-ray
  - EGD to remove retained stent (10%)

*Choksi et al. GIE 2014
**Mazaki et al. Endoscopy 2010
Pharmacoprevention

- > 35 unique agents studied
- ~ 100 clinical trials since 1977
- > 60 RCTs since 2000

- Most studies underpowered, inconsistent

- Until recently, no medication in widespread use
Can indomethacin reduce the need for pancreatic stent placement?

### Table 4. Unadjusted and adjusted risk of post-ERCP pancreatitis, by group

<table>
<thead>
<tr>
<th>Study group</th>
<th>Unadjusted risk (%)</th>
<th>Risk after risk score adjustment (%)</th>
<th>Risk after propensity score adjustment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prophylaxis (n=58)</td>
<td>20.7</td>
<td>25.7</td>
<td>23.1</td>
</tr>
<tr>
<td>PD stent alone (n=249)</td>
<td>16.1</td>
<td>15.3</td>
<td>15.7</td>
</tr>
<tr>
<td>Indomethacin and PD stent (n=247)</td>
<td>9.7</td>
<td>9.4</td>
<td>9.5</td>
</tr>
<tr>
<td>Indomethacin alone (n=48)</td>
<td>6.3</td>
<td>7.8</td>
<td>7.1</td>
</tr>
</tbody>
</table>

ERCP, endoscopic retrograde cholangiopancreatography; PD, pancreatic duct.

*Placement of pancreatic stent left to discretion of endoscopist*

*Elmunzer et al. Am J Gastro 2013*
Cholangioscopy: Sen: 86% & Spec: 55% in PSC patients
Conclusions

- Indeterminate strictures remain a clinical conundrum
- Threshold for suspicion of cancer should be low
- Use multiple tools to investigate a concerning stricture
- Consider FISH for any concerning lesion
  - Take FISH results seriously
- Cholangioscopy provides meaningful information
  - Even in the absence of a tissue diagnosis
- EUS helpful, but FNA may not be for everyone
The Timing and Type of Biliary Stenting in Pancreaticobiliary Cancer

Douglas Pleskow MD FASGE
Chief, Clinical Gastroenterology
Beth Israel Deaconess Medical Center
Associate Clinical Professor of Medicine
Harvard Medical School
Boston, MA
Malignant Pancreaticobiliary Strictures

- Pancreatic cancer
- Cholangiocarcinoma
- Gall Bladder Cancer
- Ampullary Cancer

- Metastatic Disease
  - Colon Cancer
  - Renal Cancer
  - Breast Cancer
  - Melanoma
  - HCC
  - Portal adenopathy
**Plastic Stents**

- **Materials**
  - Polyethylene, polyurethane, teflon
- **Diameter**
  - 5, 7, 8.5, 10 and 11.5 F
- **Length**
  - 3-20 cm
- **Types**
  - Straight, center bend, end bend, side ports, Tannenbaum,
  - Single and double pigtail
- **Cost** – inexpensive
- **Stent occlusion** in 30-50% after a median of 3-4 months
Metal Stents

• Materials
  - Nitinol, elgiloy
• Construction
  - Laser cut or braided
• Covering
  - silicone, polyurethane, polytetrafluoroethylene
• Differences
  - radial force, flexibility, shortening ratio, cell size, radiopacity, end design, anchoring mechanisms, ability to recapture
Metal Stents

- Diameter: 6, 8, 10 mm
- Length: 4-12cm
- Shortening ratio: 0-50%
- Deployment catheter
  - 5F–10.5F
- Cell size: 2mm - 5mm
- Stent occlusion in 15-30% after a median of 6-10 m
- Expensive

ASGE
Timing of Stent

- Preoperative
- Palliation
Timing of Stent

- Preoperative
  - Preoperative biliary drainage (PBD) was introduced in the 1970s to relieve the obstruction and to reverse physiological dysfunction resulting from obstructive jaundice
  - Only 15-20% are considered to be resectable at the time of presentation
SEMS for preoperative biliary drainage in pancreatic cancer

- Adverse events due to ERCP – 8.3%
- Stent occlusion in 5.8% after a mean of 6.6 m
- Overall survival 49% at 27 m
- Effective and safe to place SEMS in patients with pancreatic cancer preop

Siddiqui et al Dig Dis Sci 2013; 58: 1744
**SEMS or Plastic stent for preoperative biliary drainage in pancreatic cancer**

- Prospective Multicenter cohort study
- FCSEMS compared with PS from a prior RCT (van der Gaag et al. NEJM 2010)

<table>
<thead>
<tr>
<th></th>
<th>Plastic</th>
<th>FCSEMS</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>&lt; 1 week</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>53</td>
<td>103</td>
<td></td>
</tr>
<tr>
<td>Stent complications</td>
<td>31%</td>
<td>6%</td>
<td>p=0.006</td>
</tr>
<tr>
<td>Surgical complications</td>
<td>47%</td>
<td>40%</td>
<td>NS</td>
</tr>
<tr>
<td>Overall complications</td>
<td>74%</td>
<td>51%</td>
<td>NS</td>
</tr>
</tbody>
</table>

SEMS or Plastic stent for preoperative biliary drainage in pancreatic cancer

- Conclusions
  - FCSEMS is preferable to PS in patients undergoing preoperative biliary drainage
  - Occlusion and stent exchange is rare when using FCSEMS during preoperative biliary drainage
  - FCSEMS should be used routinely during preoperative biliary drainage

Current status of preoperative drainage for distal biliary obstruction

- PBD may be selectively applied in patients with severe jaundice, concomitant cholangitis, severe malnutrition, and in those who must wait for a relatively long time before surgery.
- To avoid complications, PBD should be completed with endoscopic stenting.
- Although the cost is significantly higher, metallic stenting can be utilized in patients waiting for surgery for more than 4 wk.
- Further randomized studies are required to determine the optimal PBD method for distal biliary obstruction.

Sugiyama H et al World J Hepatol 2015
How do we select patients who are suitable for PBD?

- Preoperative drainage should be performed after consideration of the following factors
  - The period of time from diagnosis to anticipated surgery
  - The presence of an urgent indication for biliary drainage; that is, acute cholangitis, severe pruritus, or severe obstruction with very high bilirubin levels
  - The functional status of the patient. Many patients are in poor status in terms of nutrition due to obstructive jaundice, which is expected to improve with PBD
  - The plan for neoadjuvant chemotherapy or chemo radiation for locally advanced or borderline resectable cancer, where PBD may prevent hepatotoxicity from chemotherapeutic agent
Distal Stricture

Metal versus Plastic

- Metal stents have much larger diameter
  - 8-10 mm vs 3 mm (10F)
  - 10 mm stents have 10X bile flow compared to 10F
- In all RCTs SEMS are associated with
  - Prolonged patency
  - Fewer repeat interventions
  - Fewer hospital days
  - Lower cost

Davids et al Lancet 1992
Kaassis et al GIE 2003
How and when to intervene

- Preoperative drainage
  - Selected cases
    - severe jaundice
    - concomitant cholangitis
    - severe malnutrition
    - those who must wait for a relatively long time before surgery
  - To avoid complications, PBD should be completed with endoscopic stenting
  - Although the cost is significantly higher, metallic stenting is advised
Meta-analysis of randomized trials comparing the patency of covered and uncovered self-expandable metal stents for palliation of distal malignant bile duct obstruction

Atif Saleem, MD, Cadman L. Leggert, MD, M. Hassan Murad, MD, Todd H. Baron, MD
Rochester, Minnesota, USA

- CSEMSs provide a significantly longer duration of patency than uncovered stents
- Rates of stent dysfunction between covered and uncovered stents are similar, but the time to re-obstruction (stent survival) is delayed with CSEMSs
- Overall complications of the two stent types are similar

Conclusion:
- The use of CSEMSs over UCSEMS for palliation of malignant distal biliary obstruction is suggested as they may potentially decrease the need for reintervention
How and when to intervene

- Palliation
  - All patients should be considered for stent
  - Plastic stent
    - Liver metastasis, Life expectancy < 3 months
  - Metal Stent
    - No liver metastasis, Life expectancy > 4 months
    - Consider CSEMS – less re-intervention
Conclusions

- Biliary obstruction needs to be individualized
- Team approach is essential
- Engage
  - GI, Surgeons, Oncologists, Interventional Radiology and Radiation Therapists
  - Co-management is essential as is constant communication
  - Establish institutional algorithm to treat the patient