PRE-INVASIVE NEOPLASIA OF BILIARY TREE
New Perspectives on Old Themes

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Emory University and Emory Winship Cancer Institute
Atlanta, GA

Disclosure
Dr. Adsay has nothing to Disclose

Overview
New perspectives on Pre-invasive neoplasia in the biliary tract
– Types, terminology, classification
– Clinicopathologic significance
I. Conventional Intraepithelial Neoplasia

1. Terminologic issues / clinical implications

<table>
<thead>
<tr>
<th>Pancreatic Intraepithelial Neoplasm</th>
<th>PanIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biliary Intraepithelial Neoplasm</td>
<td>BillIN</td>
</tr>
</tbody>
</table>

Biliary intraepithelial neoplasia: an international interobserver agreement study and proposal for diagnostic criteria

Yoh Zen1, N Volkan Adsay2, Kryztof Bardadin3, Romano Colombi4, Linda Ferreri5, Hiroshi Haga6, Seung-Mo Hong7, Prodromos Hyiroglou8, Günter Klöppel9, Gregory Y Lajweti9, Dirk I van Laarhoven10, Koichi Notohara10, Kiyoko Ohshima11, Alberto Quaglia12, Motoo Sasaki13, Fausto Sesia10, Arief Suriawinata14, Wilson Tsui16, Yutaka Aoki12 and Yasumi Nakanuma1

Review Article
A novel approach to biliary tract pathology based on similarities to pancreatic counterparts: Is the biliary tract an incomplete pancreas?

Yasumi Nakanuma
Department of Human Pathology, Kanazawa University Graduate School of Medicine, Kanazawa, Japan
**Following the trend in other organs...**

PanINs are now classified by 2-tiered approach

- PanIN-1 and 2 → Low Grade
- PanIN-3 ("CIS") → High Grade


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**BillIN/Dysplasia - Spectrum**

- **BillIN 1, 2**
- **BillIN 3**

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**BillIN/Dysplasia: Clinical significance**

- **BillIN 1, 2**
  - LOW-GRADA
  - IGNORE
- **BillIN 3**
  - HIGH GRADE
  - NOT GOOD

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**Terminology**

BillIN-3 or HGD or CIS or Carcinoma?

- **WHO**: “WHO is CIS?” (not recognized): HGD only
- **Asia**: “What is CIS, you mean ‘carcinoma, M’”?
- **Alternate** (bridging East-West): HGD/CIS
Most BilIN3 (HGD/CIS) are detected incidentally

1. Adjacent to invasive carcinoma
   – Is it at the margin, and if so, what does that mean?”
2. In a risk lesion such as choledochal cyst or PSC
   – Implications?

Most BilIN3 (HGD/CIS) is seen in ~15% of resected choledochal cysts

- Katabi and Klimstra et al, 36 cases, MSKCC experience, AJSP 2014
- Hacihasanoglu and Reid et al, 84 cases, Emory/Wayne-State, Abstract on Monday

Most BilIN3 (HGD/CIS) are detected incidentally

1. Adjacent to invasive carcinoma
   – Is there BilIN3/HGD at the margin, and if so, what does that mean?”
2. Incidentally in a risk lesion such as choledochal cyst
   – Implications?

- Sample more
- Investigate the specimen/patient carefully
- Follow up
Conventional Intraepithelial Neoplasia (IN)

2. Pathogenesis and Diagnostic issues

Inflammation \(\rightarrow\) Dysplasia \(\rightarrow\) Carcinoma sequence

Biliary Pre-invasive Neoplasia

Factors/context/etio-pathogenesis

Established risk factors:
- Parasites
- Lithiasis
- Primary sclerosing cholangitis
- Choledochal cyst
- Others

Biliary Pre-invasive Neoplasia

- Parasites
- Choledocholithiasis
- Primary sclerosing cholangitis
- Choledochal cyst
- Others

Dysplasia/Carcinoma is regeneration that has gone wrong (and has gotten out of control)

It is sometimes difficult to tell where regeneration ends and neoplastic transformation begins
Diagnostic problem #1: Replicative atypia vs Dyspl

Reperative atypia vs HGD/CIS

Diagnostic problem # 2: Colonization vs BilIN-3/CIS

II. Tumoral Intraepithelial Neoplasia
Case for discussion: 68, M
Presented with abdominal pain found to have a liver mass growing in the ductal system

Diagnosis
Intraductal tubulopapillary neoplasm (ITPN) with foci of invasive carcinoma

Tumoral IN:
Definition and significance
Intraepithelial Neoplasia

Conventional dysplastic processes such as CIN/SIL of the cervix

Mass-forming preinvasive neoplasia such as colonic adenomas

INTRAEPITHELIAL NEOPLASIA

Conventional dysplastic processes like CIN/SIL of the cervix

Mass-forming preinvasive neoplasia such as colonic adenomas

FLAT (NON-TUMORAL)  TUMORAL (ADENOMA-CA)

“Flat”  Tumoral

Not an official classification scheme, but the evolving concepts and recognized categories point towards such a distinction, in many organs
FLAT TYPE
UROTHELIAL NEOPL.
(“FLAT CIS”)
PAPILLARY
UROTHELIAL NEOPL.
(PNLUMP → LG → HG)

BIL-IN
TUMORAL IN

Tumoral IN of Biliary Tract
(Mass-forming pre-invasive neopl.)

1. IPNB (Intraductal papillary neoplasms of bile ducts; i.e., biliary counterparts of IPMN)
Biliary counterparts of IPMN: IPN-B (Intraductal Papillary Neoplasms)

**IPN-B (Intraductal Papillary Neoplasms)**

<table>
<thead>
<tr>
<th>New classification of ICC</th>
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<tbody>
<tr>
<td>Conventional type (bile duct type)</td>
</tr>
<tr>
<td>Small bile duct type (periportal type)</td>
</tr>
<tr>
<td>Well differentiated</td>
</tr>
<tr>
<td>Moderately differentiated</td>
</tr>
<tr>
<td>Poorly differentiated</td>
</tr>
<tr>
<td>Large bile duct type (peripheral type)</td>
</tr>
<tr>
<td>Well differentiated</td>
</tr>
<tr>
<td>Moderately differentiated</td>
</tr>
<tr>
<td>Poorly differentiated</td>
</tr>
<tr>
<td>Pancreatic duct type</td>
</tr>
<tr>
<td>Papillary type</td>
</tr>
<tr>
<td>Tubular type</td>
</tr>
<tr>
<td>Serous variants</td>
</tr>
<tr>
<td>Squamous cell type</td>
</tr>
<tr>
<td>Mucinous/villous cell type</td>
</tr>
<tr>
<td>Clear cell type</td>
</tr>
<tr>
<td>Undifferentiated type</td>
</tr>
<tr>
<td>Lymphoepithelial type</td>
</tr>
<tr>
<td>Others</td>
</tr>
</tbody>
</table>

**IPNB – Cellular subtypes**

| Gastric MUC5AC + | Intestinal MUC2/CDX2+ + | Biliary MUC1 + |

Clinicopathologic Features of Intraductal Papillary Neoplasm of the Bile Duct According to Histologic Subtype

<table>
<thead>
<tr>
<th>ROCHA ET AL (USA, MSKCC)</th>
<th>KIM ET AL (KOREA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GASTRIC</td>
<td>ONCOCYTIC</td>
</tr>
<tr>
<td>10%</td>
<td>15%</td>
</tr>
<tr>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>70%</td>
<td>34%</td>
</tr>
</tbody>
</table>

Intraductal Papillary Neoplasm of the Bile Duct: A Biliary Equivalent to Intraductal Papillary Mucinous Neoplasm of the Pancreas?

Kim E., Chen X., Kim J. et al.
**Clinicopathologic Features of Intraductal Papillary Neoplasm of the Bile Duct According to Histologic Subtype**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>ROCHA ET AL. (USA, MSKCC)</th>
<th>KIM ET AL. (KOREA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GASTRIC</td>
<td>10 %</td>
<td>16 %</td>
</tr>
<tr>
<td>INTESTINAL</td>
<td>5 %</td>
<td>47 %</td>
</tr>
<tr>
<td>ONCOCYTIC</td>
<td>15 %</td>
<td>3 %</td>
</tr>
<tr>
<td>PANCREATOBILIARY</td>
<td>70 %</td>
<td>34 %</td>
</tr>
</tbody>
</table>

*Intraductal Papillary Neoplasm of the Bile Duct: A*  

- Most likely definitional and selection bias  
- Partly populational?

*Parasites as the cause of IPNB: Opisthorchis viverrini and others such as clonorchis sinensis*

**Pathological characteristics of intraductal polyloid neoplasms of bile ducts in Thailand**

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2Department of Gastroenterological Surgery & Archives University Graduate School of Medicine, Sapporo, Japan  
3Department of Diagnostic Pathology, Shonan-Kenko Cancer Center, Saitama, Japan  
4Department of Pathology, Juntendo University Hospital, Tokyo, Japan

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Abstract: Intraductal papillary or tubular neoplasms of the bile duct have recently been proposed as one of the pre-invasive lesions of cholangiocarcinoma. Herein, a total of 50 cases of intraductal polyloid neoplasms of the bile ducts examined in Kanazawa University Hospital in Japan were pathologically examined. These cases previously had a history of infection of Opisthorchis viverrini. These neoplasms were histologically composed of high-grade (invasive) papillary-neoplasms showing a tubular and papillary pattern without invasion (20 cases), and with minimal and moderate invasion (13 and 26 cases, respectively). They were histologically classified into papillary type (15 cases), mucinous type (13 cases), invasive papillary type (17 cases), invasive (27 cases) and papillary-biliary type (16 cases). It was found that cases of papillary type and genetic instability were more invasive. In conclusion, intraductal papillary neoplasms in Thailand were undifferentiated papillary and/or tubular neoplasms including those with no or minimal invasion and histological and chromatin subcategorizations seem to be useful for evaluation of the aggressive pathological behaviors of these neoplasms.

**Genetic alterations of IPNB (differ slightly from pancreatic IPMNs)**

- Low frequency of KRAS mutation
  
  *Human Pathol 2003;34:902-910*

- Microsatellite instability; 10%
  
  *Mod Pathol 2002;15:1309-1317*

- Uncommon GNAS codon 201 mutation
  
  *HPB 2012;14(10):677-683*
Tumoral IN of Biliary Tract (Mass-forming pre-invasive neopl.)

1. IPNB (Intraductal papillary neoplasms- IPMN counterparts)
2. (1B?) IOPN (Intraductal oncocyic papillary neoplasms)

- Limited data: Biliary IOPNs are distinct from IPNBs
- Pancreatic IOPNs have proven to be distinct from pancreatic IPMNs (Basturk et al, Monday, poster# 267, USCAP 2016).
Subtle patterns do matter: “Pink-cell” kidney tumors

Tumoral IN of Biliary Tract (Mass-forming pre-invasive neopl.)

1. IPNB (Intraductal papillary neoplasms- IPMN counterparts)
2. (1B?) IOPN (Intraductal oncocytic papillary neoplasms)
3. ITPN (Intraductal tubulopapillary neoplasms)

The new kid on the block:
Intraductal tubulopapillary neoplasm (ITPN)
a distinct type of tumoral intra-epithelial neoplasm

ITPN: Nodular / intraductal growth
ITPN: Tubular/solid; non-mucinous

ITPNs show unusual patterns of invasion (e.g., pushing border and comedo-like)

Minimal / occasional abortive papilla

ITPN
- MUC1 ++++
- MUC6 ++
- *MUC5AC -
- MUC2 -
- Distinct molecular alterations

MUC5AC negativity is definitional, but may be not
TIN (IPNB/IOPN/ITPN) - associated invasive carcinomas are more **indolent**

1. Early detection
2. Unusual types
3. Different molecular pathways
4. Different biology

Important to recognize/report the TIN component, if present, in a case with invasive carcinoma

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**TIN-associated carcinomas Considerations**

- Sampling
- Field-effect/field defect
- Multifocality/extensiveness
  “Papillomatosis”

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**Reporting – Example of an invasive case**

I. Invasive adenocarcinoma (0.6 cm width, 0.2 cm depth), arising in an IPNB (intraductal papillary neoplasm of bile duct; 1.8 cm).

II. Invasive carcinoma is confined to the bile duct wall (pT1). No PNI; No VI.

III. IPNB is intestinal type, with extensive high-grade dysplasia.

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**Tumoral IN of Biliary Tract**
(Mass-forming pre-invasive neopl.)

1. **IPNB** (Intraductal papillary neoplasms- IPMN counterparts)
2. (1B?) **IOPN** (Intraductal oncocytic papillary neoplasms)
3. **ITPN** (Intraductal tubulopapillary neoplasms)
   - **Kindred** (conceptually very similar, a form of TIN)
   - **MCN** (mucinous cystic neoplasms with ovarian stroma)
The term HB cystadenoma/cystadenocarcinoma is a mixed bag (tainted), and should be avoided.

When defined by ovarian stroma, HB MCNs are...
- 10% of cystic hepatic lesions (rare)
- Almost all are women
- Mean age = 50
- Almost all intrahepatic (most, left lobe)
- Mean size = 11 cm (up to 23)
- 90%, low-grade
- < 10% have CIS or invasion (almost never widely invasive)

*Quigley et al, abstract, Modern Pathol, 2015

When defined by ovarian stroma, MCN (previously aka HBCA/CAC) is RARELY (10%) carcinomatous.

MCN - spectrum in lining epithelium

- Present in 80%; predominant cell type in > third
- Precursor of precursor; Predominantly mucin-poor cases are ...
  - Significantly smaller
  - In younger patients
  - Not associated with HGD or CIS

*Zhelnin and Krasinskas et al, abstract #1784, Monday
Conclusions

- HGD/CIS/BilIN-3 is clinically significant while low-grade dysplasia (BilIN 1 and 2) are difficult to define and of no verifiable significance.
- Colonization vs BilIN-3 is important and challenging.
- Choledochal cysts ought to be carefully examined (15%, HGD/CIS).

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Conclusions

- Tumoral intraepithelial neoplasms (mass-forming intraductal / intramucosal neoplasms) represent “adenoma-carcinoma sequence”.
- ~10% of biliary cancers arise from TINs.

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Conclusions

- IPNBs have multiple cell lineages. ~60% are invasive at resection.
- Oncocytic ones (IOPNs) appear to be distinct (less propensity for invasive behavior).
- Multifocality / field-defect (effect) phenomenon are important. Thorough sampling is crucial.
- Biliary ITPN (tubulo-papillary) is now recognized as a distinct category.
- MCN, defined as ovarian stroma is rare, almost all are women and intrahepatic, and seldom show carcinomatous transformation. Non-mucinous epithelium may reflect early version (precursor of precursor).