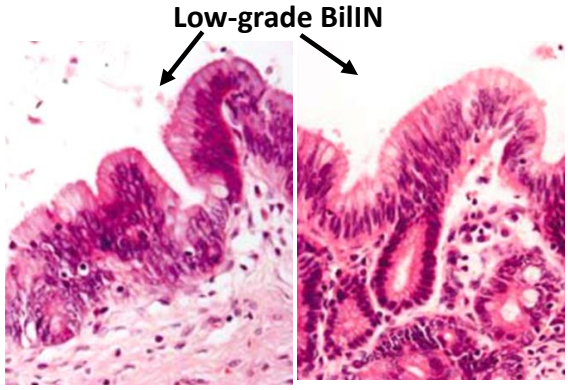
Tumors of the Gallbladder and Bile Ducts

Benign Tumors

Biliary Intraepithelial Neoplasia (BilIN)



Non-invasive (in situ) dysplastic epithelial lesion within the biliary tree or gall bladder.
Can be low-grade or high-grade.

Chronic inflammation (e.g., with stones, PSC, or parasite) can induce mutations→ dysplasia→ cancer

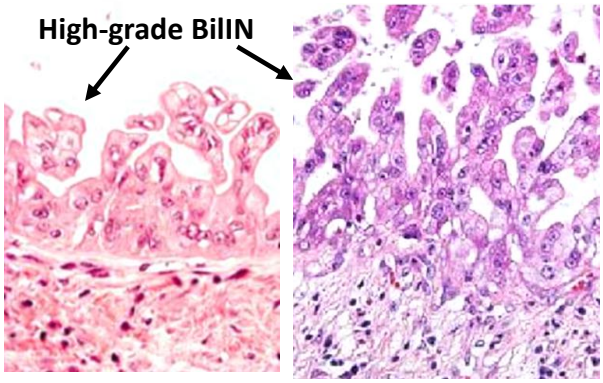
Molecular: KRAS mutations seen in ~40% cases, TP53 mutations are a late event in high-grade BilIN

Two-tiered grading system (see table below), grade the area of *worst* cytoarchitectural atypia

Architecture can be flat or micropapillary.

Can colonize peribiliary glands and Rokitansky-Aschoff sinuses→ don't confuse for invasion!!

*Factors favoring **reactive atypia**:*
- Cellular atypia is worse deeper in the epithelium and "matures" as you approach the surface
- Nuclei have fine chromatin
- Gradual transition from normal to atypical (neoplastic processes often have an abrupt transition)



Feature		Low-grade BilIN (BilIN 1/2)	High-grade BilIN (BilIN 3)
Microscopic findings		Flat or micropapillary Hyperchromatic nuclei Increased N:C ratio Nuclear stratification Preserved nuclear polarity	Flat or micropapillary Hyperchromatic and irregular nuclei Pleomorphic cells with bizarre nuclei Increased N:C ratio Complex nuclear stratification Loss of nuclear polarity
Biliary mucosa involvement		Relatively focal	Relatively extensive
Involvement of peribiliary glands		Uncommon	Common
IHC	Ki67	Low to intermediate	Frequently high
	S100	Mild to moderate	Diffuse and strong
	p53	Wild-type	Abnormal (Diffuse strong or null)
	p16	Preserved	Decreased

Note: On cytology specimens (e.g., bile duct brushing), the distinction between invasive and non-invasive disease cannot be distinguished, so BilIN3 appear identical to invasive carcinoma.

Outcomes: If confined to gallbladder, cured by surgical excision.

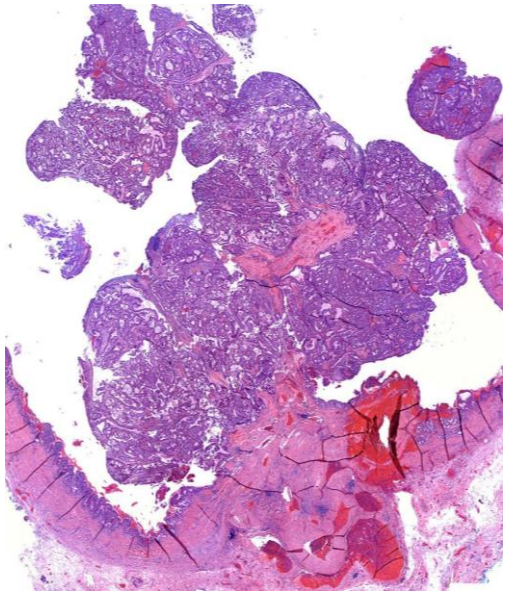
However, this can be a "field defect" with multifocal disease throughout the biliary tree with regional recurrences.

Modified from: WHO Classificaiton of Tumours: Digestive System Tumours. 5th Ed.

Intracholecystic Papillary Neoplasm

(Essentially an IPMN, but in the gallbladder!)

A **mass-forming (grossly visible), non-invasive neoplasm arising in the gallbladder mucosa.** (vs BilIN, which is microscopic)



Intraluminal growth of back-to-back epithelium with primarily **papillary architecture** (sometimes tubulopapillary)

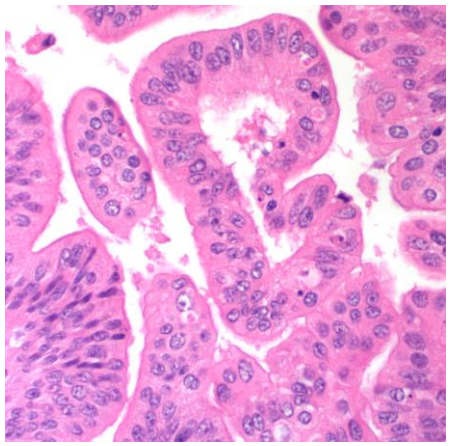
Grade dysplasia using same criteria as BilIN
Often adjacent BilIN; Frequent KRAS mutations.

Four morphological patterns, often intermixed, with no current clinical significance:
Biliary→ Most common, cuboidal cells with clear to pink cytoplasm, enlarge nuclei, and frequent nucleoli
Gastric→ Resemble foveolar cells (tall with abundant apical mucin)
Intestinal→ Resemble colonic adenomas
Oncocytic→ Least common, abundant eosinophilic granular cytoplasm

An **invasive carcinoma is identified in ~1/2 of cases** (especially biliary type with high-grade BilIN), so sample completely!

Intraductal Papillary Neoplasm of the Bile Ducts (Biliary IPMN)

Grossly visible papillary lesion predominantly growing in the bile duct lumen (vs BilIN, which is microscopic—*not* grossly visible)
→ Can cause biliary obstruction→ Duct dilation
→ Can secrete abundant mucus



Papillary fronds with fine fibrovascular cores covered by cuboidal or columnar neoplastic epithelium with variable cytologic atypia
Grade based on area of worst atypia

Risk factors: PSC, Liver flukes

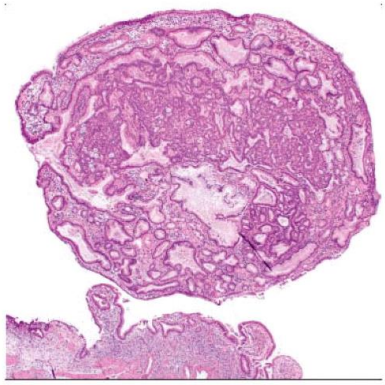
Molecular: KRAS mutation→ Low-grade dysplasia→ P16 loss, TP53 mutation→ High-grade dysplasia→ Invasive carcinoma

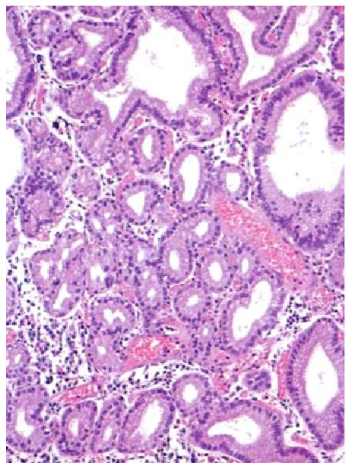
Can subgroup same as above (ICPN), but often mixed

Outcome: ~50% have an associated invasive component, so sample well. Still, better prognosis than conventional cholangiocarcinoma

Pyloric gland adenoma of the Gallbladder

Non-invasive, benign glandular neoplasm of the gallbladder composed of **mucinous glands with pyloric to Brunner's gland features**
- small, tightly packed bland-looking glands with abundant pale apical mucinous cytoplasm, peripheral nuclei, and minimal intervening stroma.
- Some glands may be cystically dilated.





Can be pedunculated or sessile

Rarely, can have superimposed high-grade dysplasia or carcinoma.

Malignant Tumors

Carcinoma of the Gallbladder

Malignant epithelial neoplasm in the gallbladder arising from the biliary epithelium
Most common biliary tract malignancy, most frequent in old women (long-standing gallstones)

Tumors are most often located in the fundus and flat.
Signs and symptoms overlap with cholelithiasis, often diagnosed incidentally.

Risk factors: Gallstones (most common), PSC, certain regional SNPs
Inflammation (chronic cholecystitis→ calcifications→ "Porcelain gallbladder")→ BilIN→ Carcinoma
Most cases are associated with surrounding dysplasia, so if you find dysplasia, sample the gallbladder well to see if there is an occult carcinoma!

Molecular: Frequent CTNNB1 (β-catenin) mutations, sometimes HER2 amplified or MMR-deficient

Subtypes:
Biliary-type Adenocarcinoma: Most common subtype. Similar in morphology and behavior to pancreatic ductal adenocarcinoma. Infiltrating tubules lined but cuboidal cells in desmoplastic stroma.

Intestinal-type Adenocarcinoma: Resemble colonic adenocarcinomas. Tubular configuration with columnar cells with elongated, pseudostratified cells. Rare→ must rule out a metastasis

Mucinous Adenocarcinoma: >50% of the tumor contains abundant extracellular mucin.

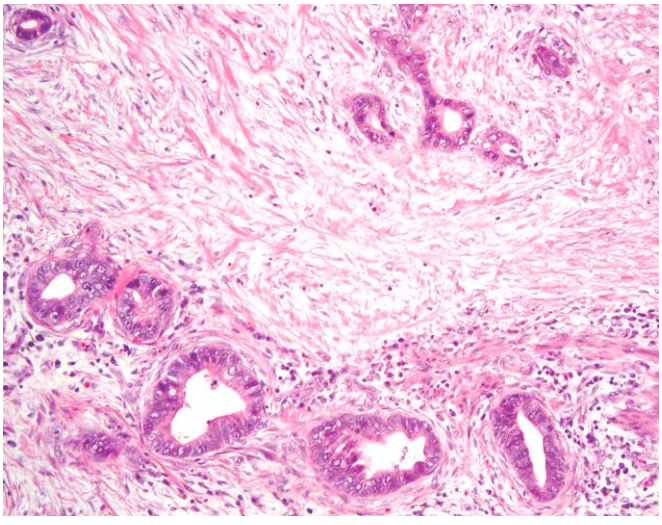
Poorly-cohesive carcinoma: Individual cells infiltrating diffusely through wall. Includes Signet-ring cells.

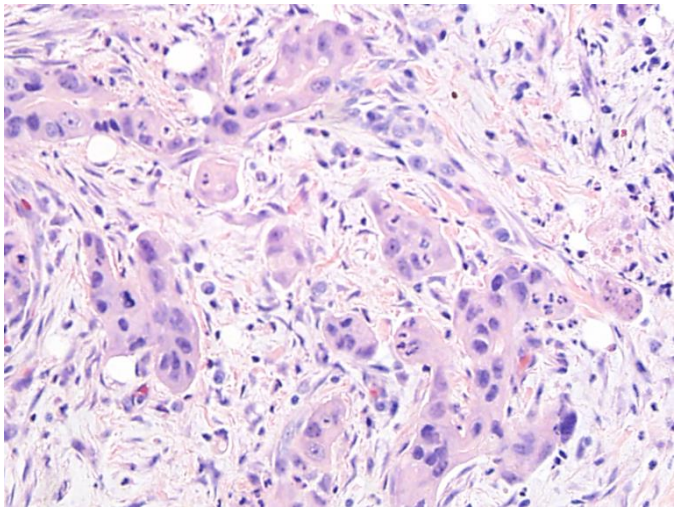
Other subtypes: Clear cell carcinoma, Squamous cell carcinoma, Adenosquamous carcinoma,

It can be hard to tell dysplasia involving a Rokitansky-Aschoff sinus from invasive tumor. Invasive tumor glands are often smaller glands with irregular contours and increased cytologic atypia. In contrast, RA sinuses are often larger, dilated, and have round contours.

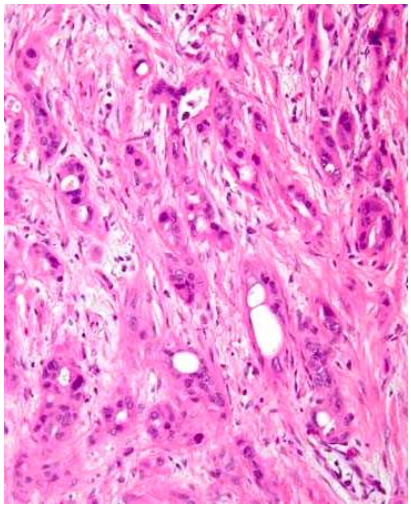
Prognosis depends largely on stage:
If "Early" (not yet muscle invasive, so pTis/T1a/T1b)→ Good prognosis
If "Advanced" (Into or beyond muscle, ≥pT2)→ Aggressive

Note: pT2 is subdivided by if the tumor is on the hepatic or peritoneal side of the gallbladder:
pT2a→ Peritoneal side → Relatively better prognosis
pT2b→ Hepatic side → Relatively worse prognosis





Carcinoma of the Extrahepatic Bile Ducts



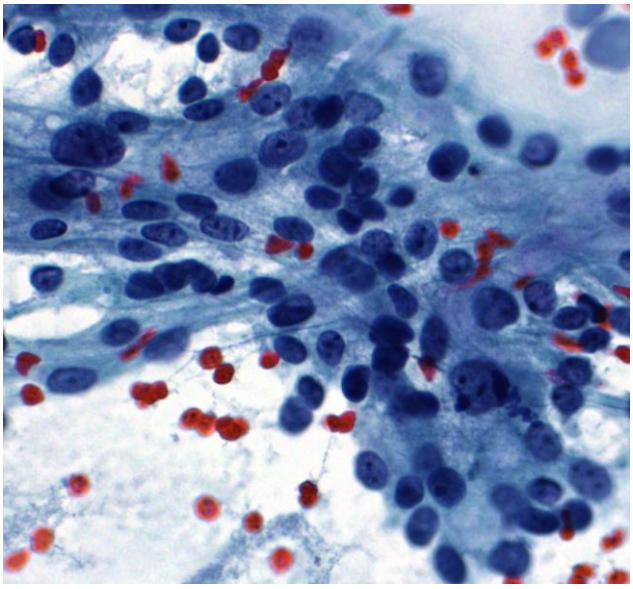
Malignant epithelial neoplasms arising in the extrahepatic bile ducts.
Most frequently **Adenocarcinoma** = ***Cholangiocarcinoma***
Klatskin tumor: Perihilar tumor occurring at the confluence of right and left hepatic ducts

Often older patients **presenting with obstructive jaundice**
Risk factors: PSC, Liver flukes, Choledochal cysts, and Gallstones

Two precursor lesions: BilIN and **Intraductal papillary neoplasms**
Molecular: Early KRAS mutations. Frequent late TP53 mutations.

Most carcinomas are pancreatobiliary-type: resemble pancreatic ductal adenocarcinoma. Widely-spaced, irregular glands and small tumor clusters infiltrating through desmoplastic stroma. Frequent perineural and lymphovascular invasion.

Overall, very aggressive tumors with poor prognosis



Cytologic Diagnosis of Adenocarcinoma:

Since it so closely resembles pancreatic ductal adenocarcinoma, we use the same cytologic criteria *(best seen on Pap-stained slides):*

1) Nuclear pleomorphism (>4:1)
2) Architectural disarray ("drunken honeycomb")
3) Irregular nuclear contours
4) Single malignant cells

Helpful additional clue: A clearly neoplastic population and a separate distinct clearly benign population.

If the person has PSC or a Stent, they may have considerable reactive atypia, so, in these cases, it is often prudent to be more conservative and consider downgrading your diagnoses accordingly.

Ancillary testing on cytology specimens:
1) Next-gen sequencing→ looking for KRAS or TP53 mutations, etc..
2) FISH (e.g., Urovysion) looking for aneuploidy

NOTE: The distinction between high-grade BilIN (non-invasive) and invasive carcinoma cannot be made by brush cytology.

Some advanced endoscopists can get tissue biopsies from common bile duct lesions via cholangioscopy (e.g., with "Spyglass"), often yielding small biopsies.