LIVER AND GALLBLADDER CANCERS

Kenneth Alonso, MD, FACP

LIVER

Hepatocellular adenoma

- Women, principally
- 20-40 years of age.
- Oral contraceptives are thought to be an etiologic factor as well as are anabolic steroids.
- Regress when hormones withdrawn.
- May rupture during pregnancy
- It is also seen in those with glycogen storage disease Ia and with Fanconi anemia.
- Generally solitary and in the right lobe
- Often large when identified.
- Cold (no uptake) on Technetium-albumin scan (lack Kupffer cells).

Hepatocellular adenoma

- Five subtypes:
- (1) Inactivating mutations of HNF1-α (HA-H, 35%)
- 90% are somatic mutations of TCF1 (HNF1A) gene
- < 5% heterozygous germline mutations of CYP1B1 gene
- Resultant increase in lipogenesis by promotion of fatty acid synthesis and by downregulation of liver type fatty acid binding protein (LFABP)

Hepatocellular adenoma

- Germline mutation responsible as well for Maturity onset diabetes of youth type 3 (MODY-3).
- Somatic mutation necessary as well in MODY-3 if hepatocellular adenoma to develop.
- Microscopic examination:
- Steatosis.
- Some areas show. prominent pericellular staining or almost complete circling of small groups of hepatocytes by reticulin fibers

Hepatocellular adenoma

- (2) Inflammatory (HA-I, 35%)
- Associated with Non-alcoholic fatty liver disease
- Activating mutation of IL6ST gene producing gp130 (IL-6 co-receptor); leads to constitutive JAK-STAT signaling
- Microscopic examination:
- Irregular, poorly circumscribed borders; inflammatory infiltrates and sinusoidal dilatation; may have "pseudoportal tracts," which are islands of thick walled arteries with no definite bile ducts but associated ductular reaction .
- Express C-reactive protein and serum amyloid A

Hepatocellular adenoma

- (3) β-catenin activation (HA-B, 10%)
- Mutations in exon 7 - 8 and exon 3 result in stabilization of β-catenin protein and increased or non-transient activation of WNT/β-catenin signaling pathway
- Glutamine synthetase (target for β-catenin) diffusely elevated
- Very high risk for malignant transformation

Hepatocellular adenoma

- Microscopic examination:
- Pseudoacinar arrangement
- Cytologic abnormalities including nuclear pleomorphism and atypia, multinucleation, prominent nucleoli
- Steatosis is rare
- No significant inflammation

Hepatocellular adenoma

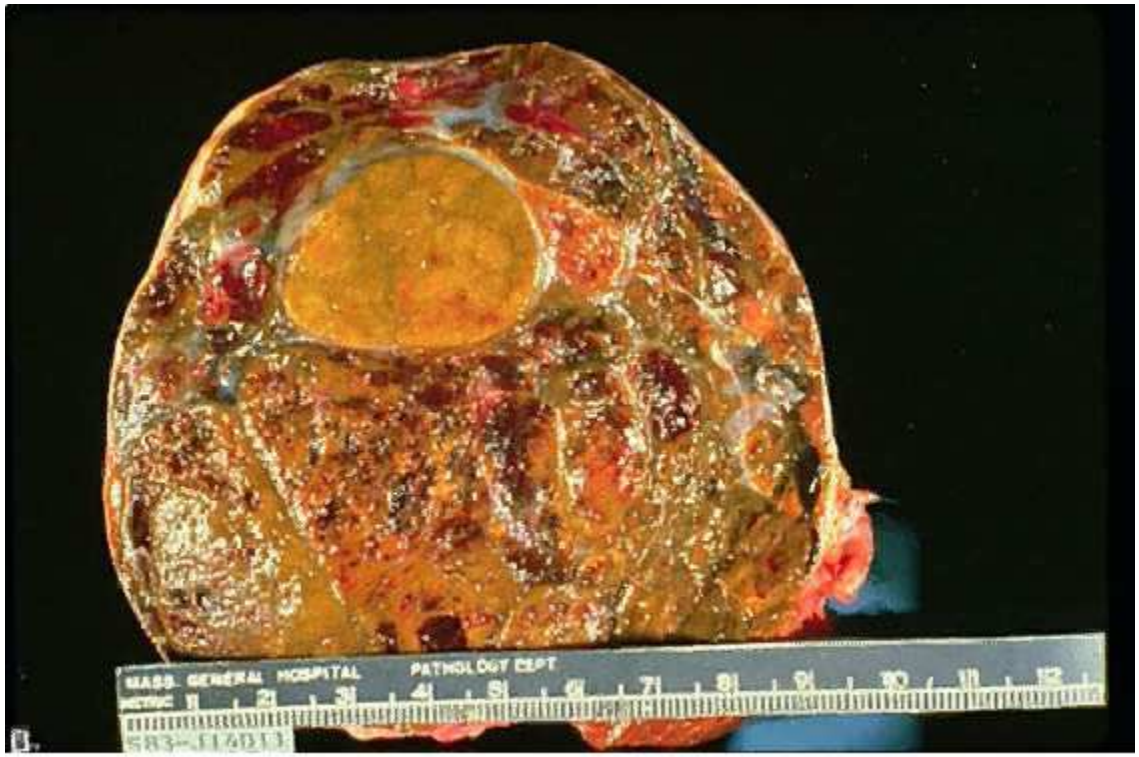
- (4) Sonic hedgehog (SHH) mutated (HA-sh, 5%)
- Activation of sonic hedgehog pathway via fusion of promoter of INHBE with GLI1
- Also upregulation of argininosuccinate synthase 1, which may indicate increased risk of hemorrhage
- (5) Unspecified (HA-U, 7%)
- Morphology characteristic of adenoma but no specific characteristics of the individual subtypes
- Lesions with extensive hemorrhage and necrosis are currently grouped into this subtype

Hepatocellular adenoma

- Risk of malignant transformation:
- Male sex
- β-catenin mutation
- Large tumors

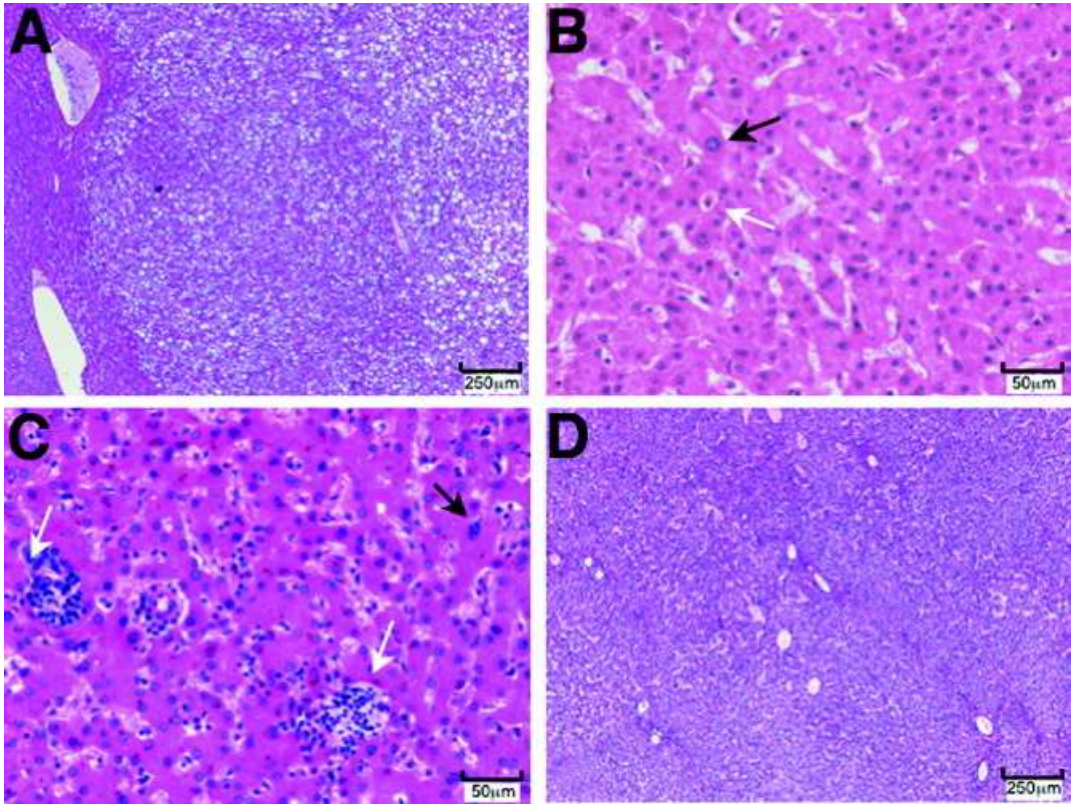
- Treatment:
- Surgical excision if tumor in man, irrespective of size
- Surgical excision in women if tumor >5cm and there are β-catenin mutations
- Else, withdraw oral contraceptives and follow

Hepatocellular adenoma



(Courtesy of L Friedman.) Fig. Ch. 16

Zucman-Rossi, J, Jannot, E, Tran Van Nhieu, J, et al, “Genotype–phenotype correlation in hepatocellular adenoma: New classification and relationship with HCC”, **Hepatology, Volume: 43, Issue: 3, Pages: 515-524, First published: 22 February 2006, DOI: (10.1002/hep.21068)**



Main characteristic morphological features in adenomas. (A) Typical aspect of a HNF1α–mutated adenoma with marked steatosis, no cytological abnormalities, and no inflammatory infiltrate. (B) A β-catenin–activated adenoma presenting pseudo-glandular formation (white arrow) and some cytological abnormalities with hyperchromatic nuclei (black arrow) (C) Adenoma with neither HNF1α nor β-catenin mutations presenting focal inflammatory infiltrate (white arrow) and some cytological abnormalities with hyperchromatic nuclei (black arrow) (D) Adenoma with neither HNF1α nor β-catenin mutations and without any morphological particularities: no steatosis, no cytological abnormalities, and no inflammatory infiltrate

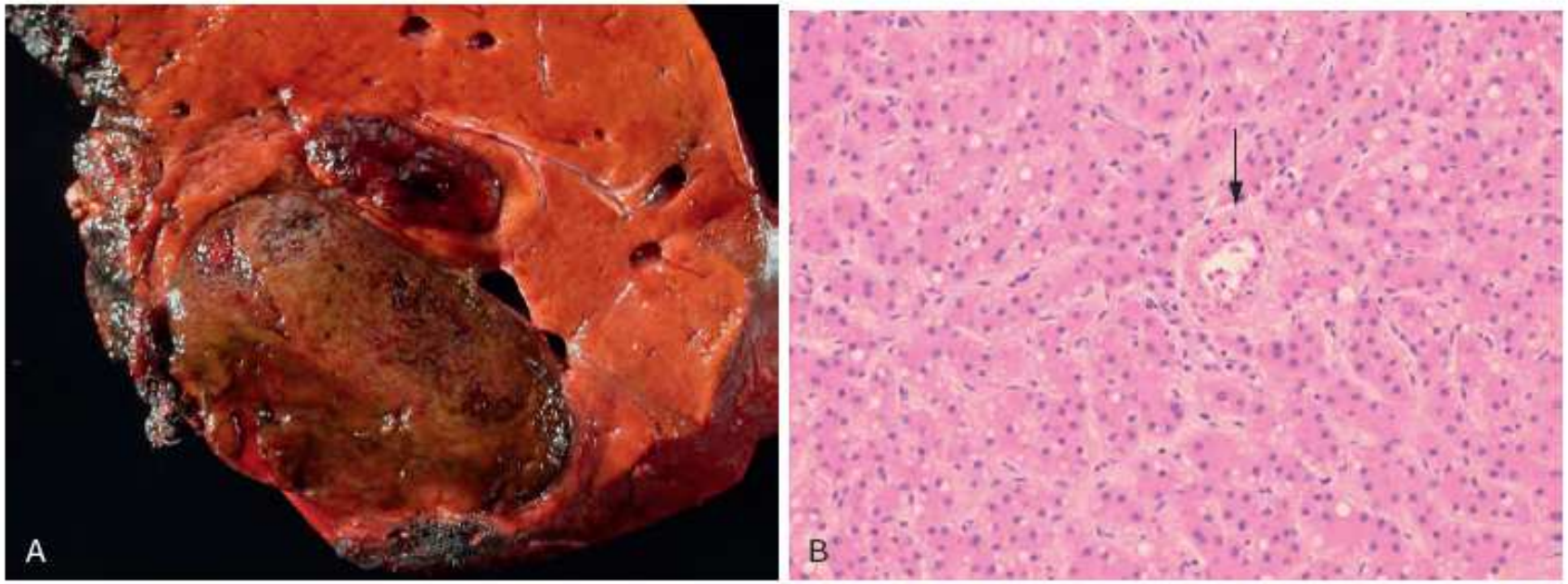
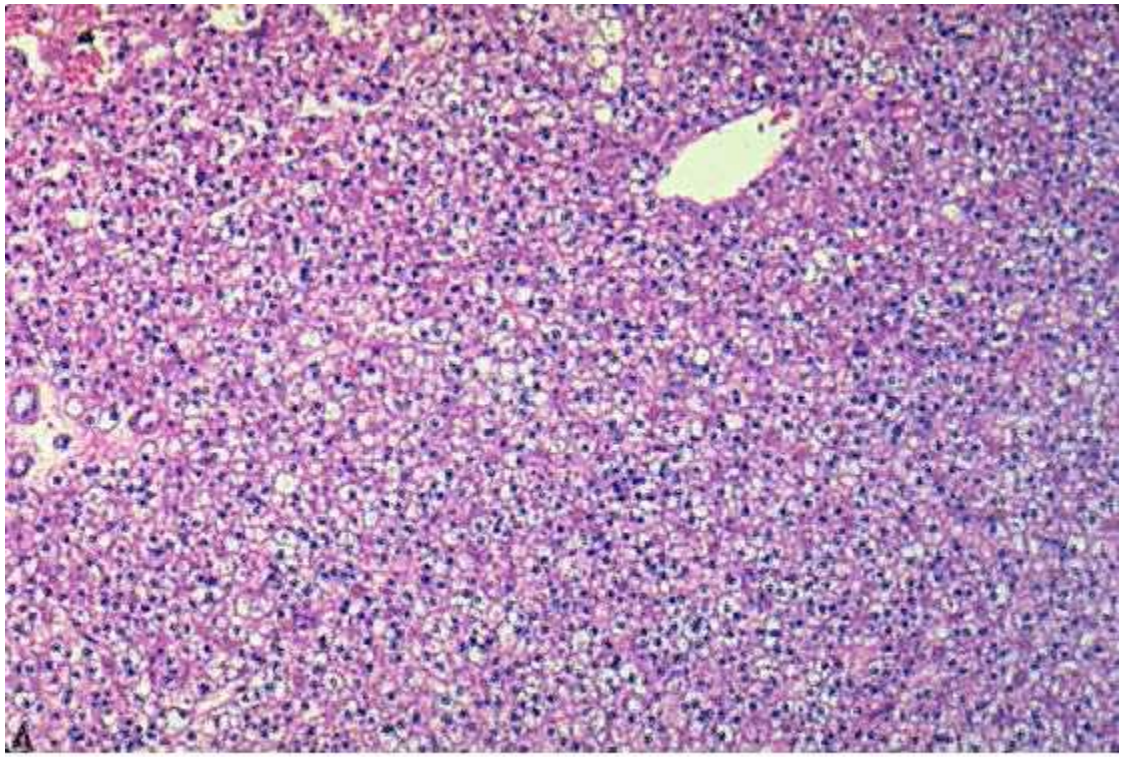


Figure 18-53 Liver cell adenoma. **A,** Resected specimen presenting as a pendulous mass arising from the liver. **B,** Microscopic view showing cords of hepatocytes, with an arterial vascular supply *(arrow)* and no portal tracts.

Hepatocelluar adenoma



Courtesy of (L Friedman.) Fig. Ch. 16

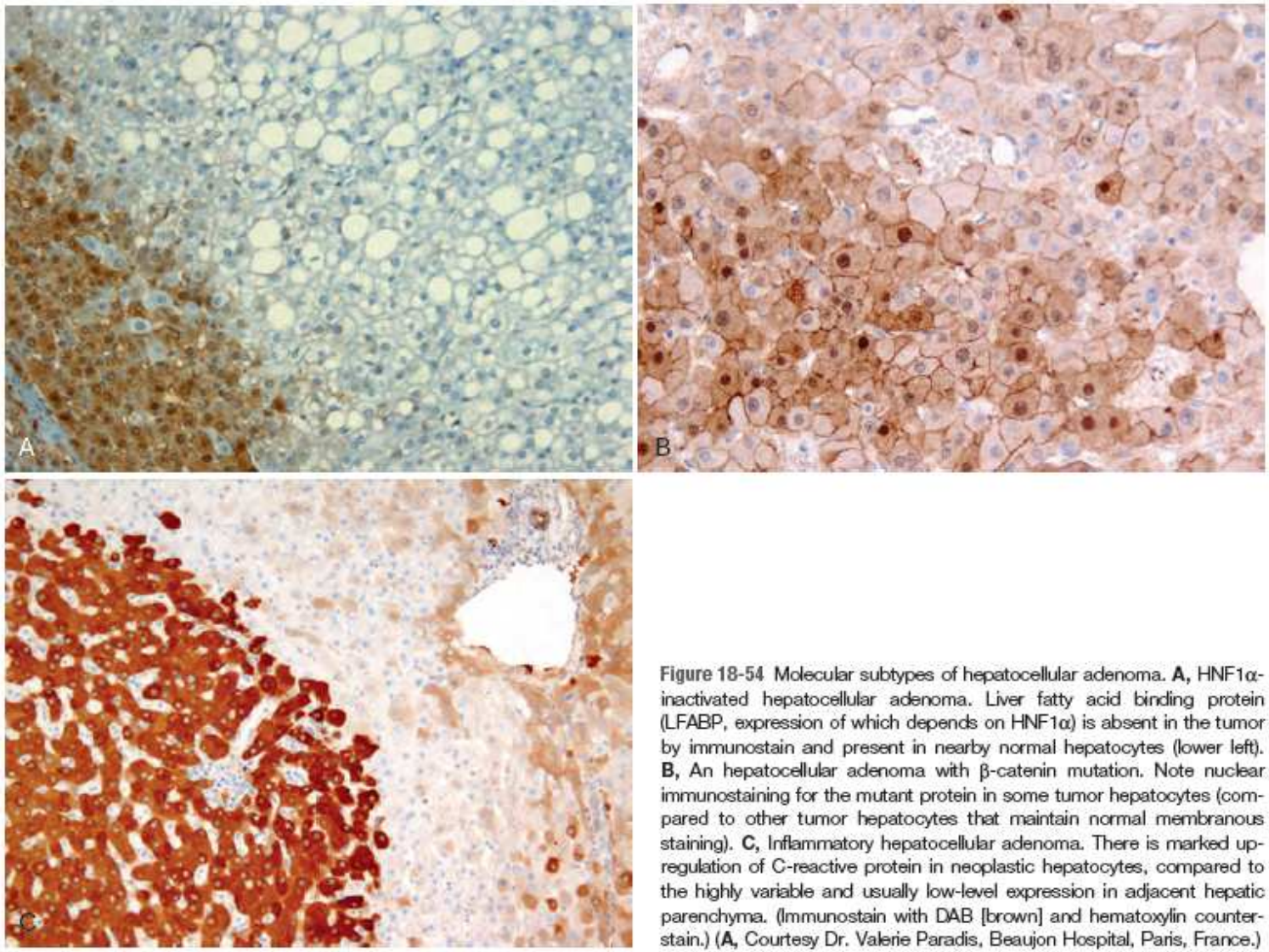


Figure 18-54 Molecular subtypes of hepatocellular adenoma. **A,** HNF1α-inactivated hepatocellular adenoma. Liver fatty acid binding protein (LFABP, expression of which depends on HNF1α) is absent in the tumor by immunostain and present in nearby normal hepatocytes (lower left). **B,** An hepatocellular adenoma with β-catenin mutation. Note nuclear immunostaining for the mutant protein in some tumor hepatocytes (compared to other tumor hepatocytes that maintain normal membranous staining). **C,** Inflammatory hepatocellular adenoma. There is marked up-regulation of C-reactive protein in neoplastic hepatocytes, compared to the highly variable and usually low-level expression in adjacent hepatic parenchyma. (Immunostain with DAB [brown] and hematoxylin counterstain.) (**A,** Courtesy Dr. Valerie Paradis, Beaujon Hospital, Paris, France.)

Hepatocellular carcinoma

- Most common liver cancer
- High incidence in Asia secondary to HBV as well as aflatoxin use
- Incidence in US related to HCV
- 50-60 years of age
- Men (3-8:1)
- Over one-third are asymptomatic
- Abdominal pain
- Fever (due to liver cell necrosis)
- Rapid liver enlargement in a cirrhotic patient
- May be focal, multifocal, or diffusely infiltrating
- Commonly invade portal and hepatic veins

Hepatocellular carcinoma

- Intrahepatic metastases
- Become more likely once tumors reach 3 cm in size.
- Metastases are usually small, satellite tumor nodules around the larger, primary mass.
- The vascular route is also the most likely route for extrahepatic metastasis, especially by the hepatic venous system.
- Hematogenous metastases, especially to the lung, tend to occur late in the disease.
- Occasionally invade the portal vein (causing portal hypertension) or inferior vena cava. The latter can even extend into the right side of the heart.
- Lymph node metastases are less common

Hepatocellular carcinoma

- Causes include:
- Post-necrotic cirrhosis due to chronic HBV or HCV infection
- Alcoholic cirrhosis
- Non-alcoholic fatty liver disease
- Non-alcoholic steatohepatitis
- Aspergillus aflatoxin (peanuts, mold)
- Hereditary hemochromatosis
- Wilson's disease
- α_1-antitrypsin deficiency
- Primary biliary cirrhosis

Etiology of HCC at the Molecular Level

	EGFr	RAF	Telomerase	DNA methylation	p53
HBV			●		
HCV	●	●			
EtOH				●	
Obesity	●				●

Thorgeirsson, S; et al. Nature Genetics, 31: 2002

Hepatocellular carcinoma

- AFP elevated (the cancer assay is not the same one utilized in obstetric cases to evaluate fetal state)
- May produce:
- Erythropoietin
- Insulin-like factor
- Parathormone related protein
- Fibrolamellar variant (5%) occurs in those 20-40 years of age without underlying liver disease.

Hepatocellular carcinoma

- Hepatocellular carcinoma associated with HBV.
- HBV X-protein, a transcriptional activator, main promoter of cellular transformation. PKC and NF-κB stimulated.
- Hepatocellular carcinoma caused by HCV is not common in HBV prevalent populations.

Hepatocellular carcinoma

- Hepatocellular carcinoma associated with HCV.
- (Core protein localizes in outer mitochondrial membrane and endoplasmic reticulum, promoting oxidative stress. The non-structural proteins NS3 and NS5A also promote oxidative stress.)
- HCV induces TNF-α related insulin resistance.
- Alcohol potentiates oxidative stress; it also leads to changes in the hyper-variable region of the HCV genome and is associated with resistance to interferon-α.

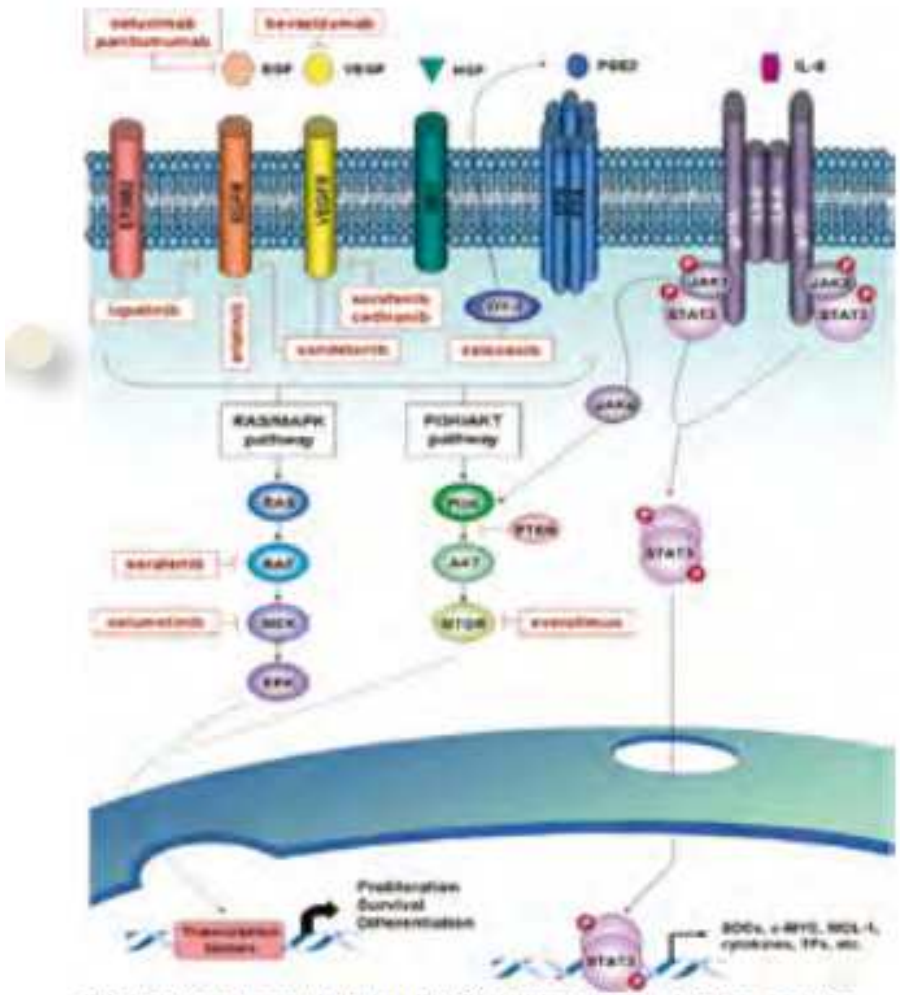
Hepatocellular carcinoma

- Alcohol inhibits the expression of BCL-2 in hepatocytes.
- Aflatoxin leads to p53 loss
- TGF-β induced apoptosis depressed.
- May arise from liver stem or fetal cells
- Thought to promote tumor formation in the cirrhotic liver.
- MYC , C-MET, and HH abnormalities also noted.
- p53, p27, p16 functions lost in cirrhosis as well.

Hepatocellular carcinoma

- Wnt/β-catenin and PI3K/Akt pathways activated in 50% of hepatocellular cancers.
- Early mutational event
- Loss of p53 is an early event as well
- Small cell change is thought to be directly premalignant.
- Large cell change is at least a marker of increased risk of cancer in the liver as a whole, but in hepatitis B they may also be directly premalignant.
- Dysplastic nodules are found in cirrhosis.

The main mutations in hepatocarcinogenesis include the tumor suppressor gene TP53 and the beta-catenin gene. Molecular profiling of HCC has shown alteration of many signaling cascades: epidermal growth factor receptor (EGFR) and RAS signaling, mTOR, insulin-like growth factor 1 (IGF-1), hepatocyte growth factor (HGF) and C-MET pathways.



EGF, Epidermal growth factor; EGFR, epidermal growth factor receptor; HGF, hepatocyte growth factor; IL-6, interleukin-6; IL-6-R, interleukin-6 receptor; PGE2, prostaglandin 2; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

Table 18-12 Precursor Lesions of Hepatocellular Carcinoma and Cholangiocarcinoma

	Hepatocellular Carcinoma					Cholangiocarcinoma		
	Hepatocellular Adenoma	Small Cell Change	Large Cell Change	Low Grade Dysplastic Nodule	High Grade Dysplastic Nodule	BilIN-3	Mucinous Cystic Neoplasm	Intraductal Papillary Biliary Neoplasia
Focality in liver	Single or multiple (adenomatosis)	Diffuse	Diffuse	Single or multiple	Single or multiple	Diffuse or multifocal	Single	Focal or diffuse
Premalignant	Yes	Yes	In some HBV*	Uncertain*	Yes	Yes	Yes	Yes
Association with cirrhosis	Rare	Common	Common	Usual	Usual	Sometimes	No	No
Commonly associated diseases	NAFLD, Sex hormone exposures Glycogen storage diseases	HBV, HCV, Alcohol, NAFLD, A1AT, HH, PBC	HBV, HCV, Alcohol, NAFLD, A1AT, HH PBC	HBV, HCV, Alcohol, NAFLD, A1AT, HH PBC	HBV, HCV, Alcohol, NAFLD, A1AT, HH PBC	PSC, Hepatolithiasis, Liver flukes	None	None
Occurrence without identified predisposing condition	Occasional	No	No	No	No	Yes	Yes	Yes
Need for surveillance cancer screening	± depending on presence of predisposing condition	Yes	Yes	Yes	Yes	Yes	No	Yes

*While these are not certain to be directly premalignant, they are always at least an indication of increased risk for malignancy in the liver as a whole.
BilIN-3, Biliary intraepithelial neoplasia, high grade; NAFLD, nonalcoholic fatty liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; A1AT, α_1-antitrypsin deficiency; HH, hereditary hemochromatosis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.

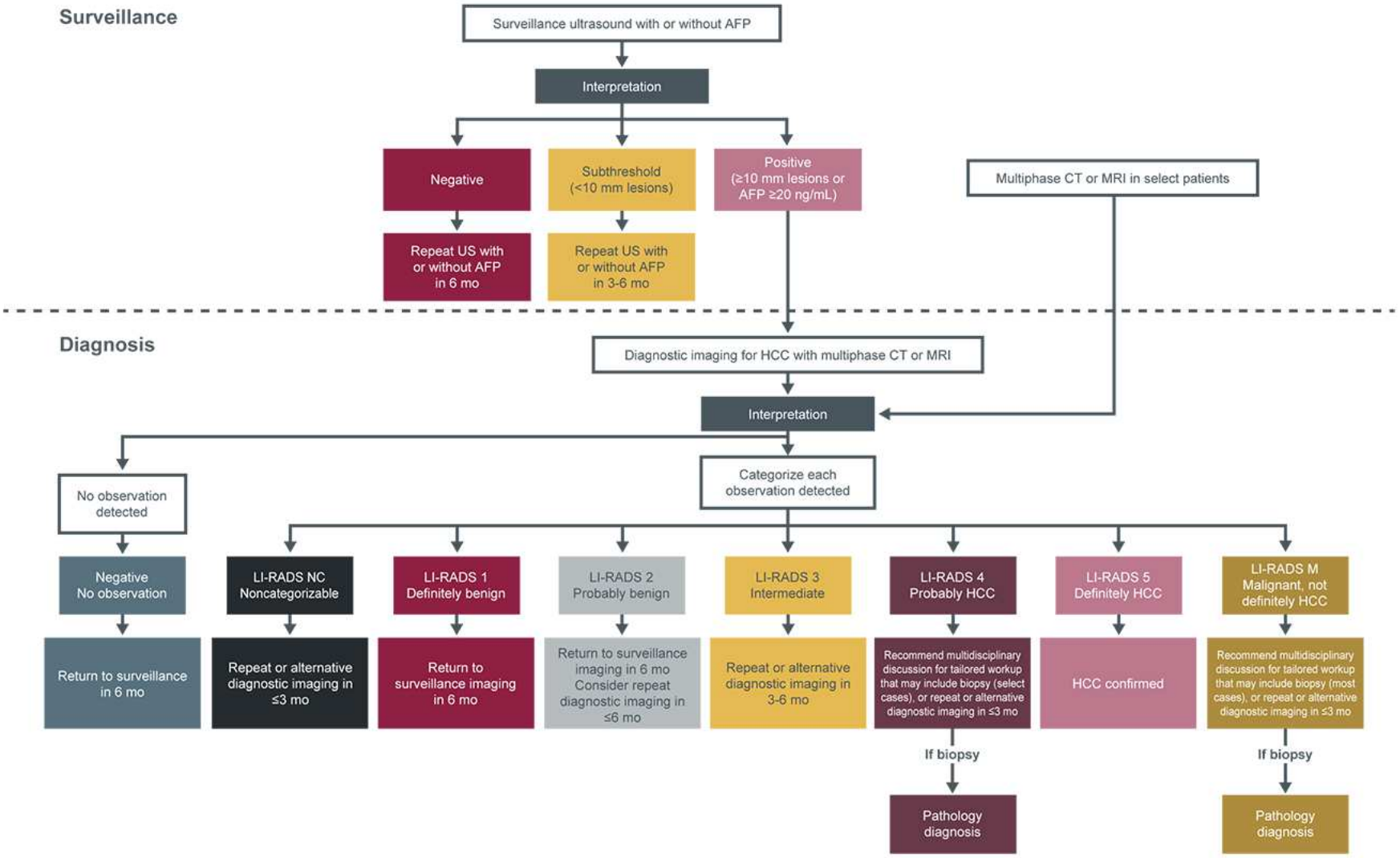
Screening criteria

- Screen all who have a history of Hepatitis C
- Screen all Asian men over 40 years old who have a history of Hepatitis B; Asian women, over 50 years old
- Screen HBV carriers and those with HBV and HIV
- Screen all with cirrhosis
- AFP and Ultrasound are used together
- AFP >100, likely malignancy
- Ultrasound mass >10mm size, likely malignant
- Active viral infection reduces image quality
- If lesion >10mm or AFP>20, screen with dynamic enhanced contrast MRI or CT

Liver imaging reporting

- LR-1 angioma, focal fibrosis, scar, cyst likely
- LR-2 also, cirrhotic nodule
- LR-3 with or without arterial phase enhancement
- Approximately one third are malignant (biopsy)
- LR-M, target lesion not characteristic of hepatocellular carcinoma
- Approximately one third are malignant (biopsy)
- LR-4 no arterial phase or no rim arterial phase enhancement
- Approximately 80% of masses are malignant
- LR-5 enhancing capsule
- Approximately 97% of masses are malignant

Figure 5: AASLD Algorithm for HCC Surveillance and Diagnosis



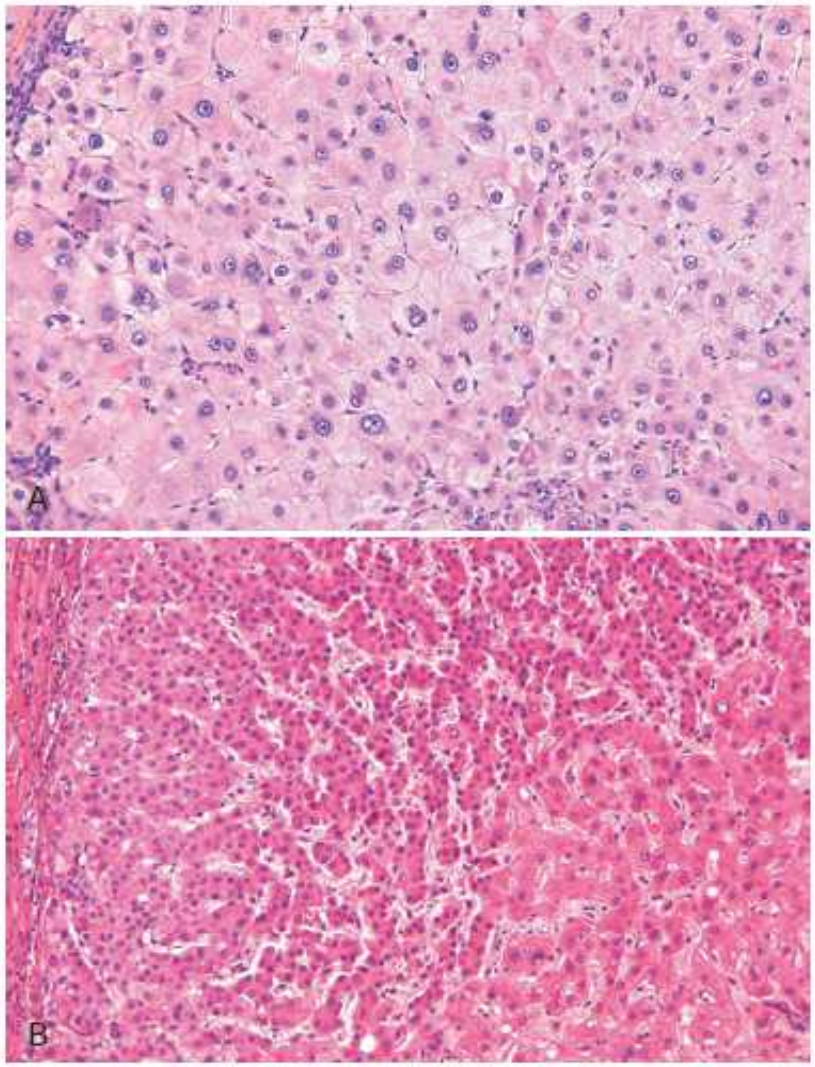


Figure 18-57 **A,** Large cell change. Large hepatocytes with large, often atypical nuclei are scattered among normal-size hepatocytes with round, typical nuclei. **B,** Small cell change. The abnormal cells have a high nuclear-to-cytoplasmic ratio and are separated by thickened plates. Normal-appearing hepatocytes are in the lower right corner. (Courtesy Dr. Young Nyun Park, Yonsei Medical College, Seoul, South Korea.)

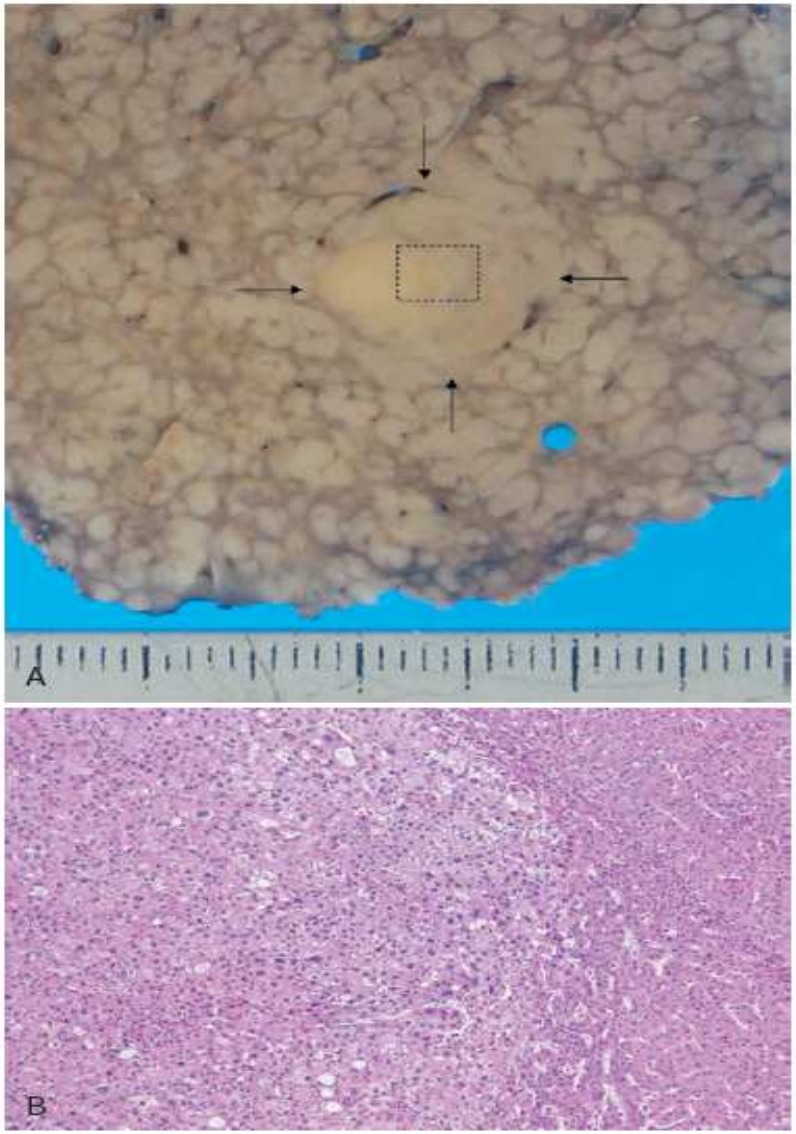
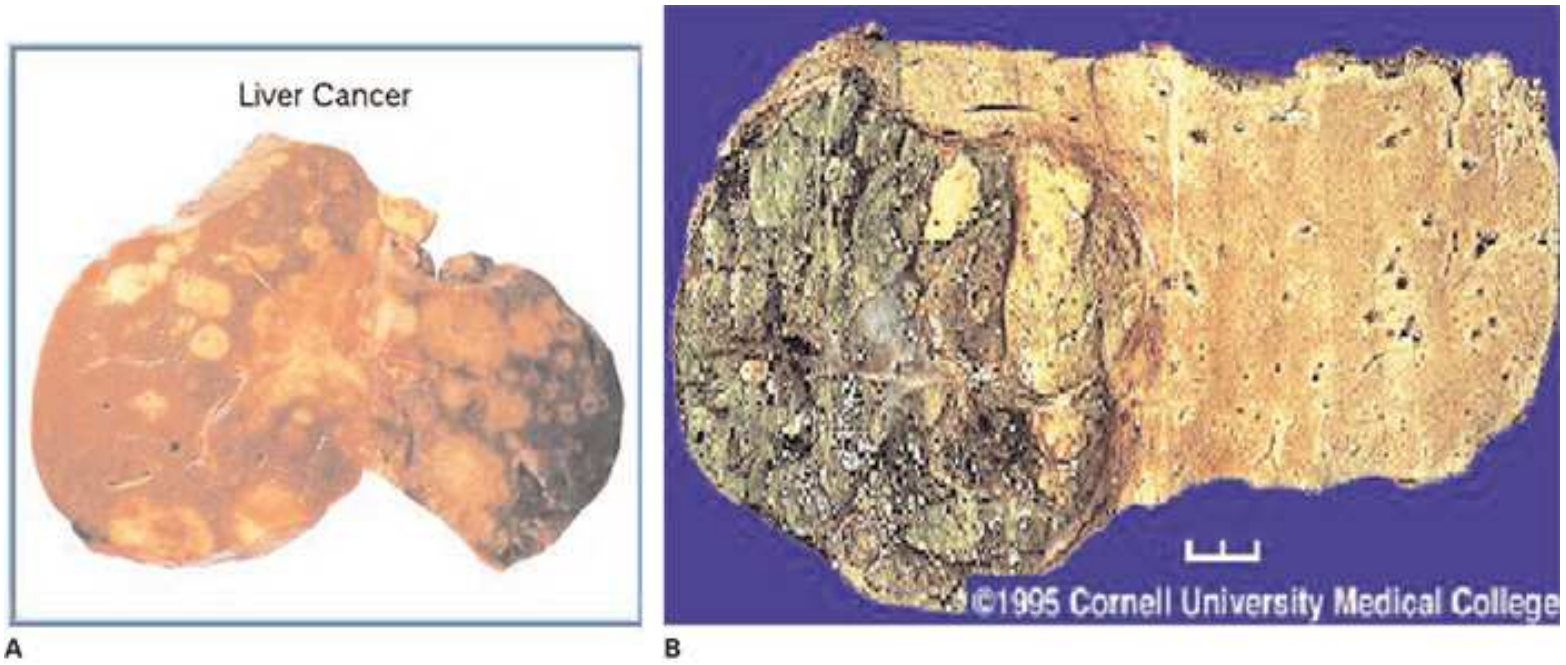


Figure 18-58 **A,** Hepatitis C–related cirrhosis with a distinctively large nodule *(arrows)*. Nodule-in-nodule growth suggests an evolving cancer. **B,** Histologically the region with in the box in **A** shows a well-differentiated hepatocellular carcinoma (HCC) (right side) and a subnodule of moderately differentiated HCC within it (center, left). (Courtesy Dr. Masamichi Kojiro, Kurume University, Kurume, Japan.)

Hepatocellular cancer



A B

Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com

Fig. 15-9 Accessed 04/10/2010

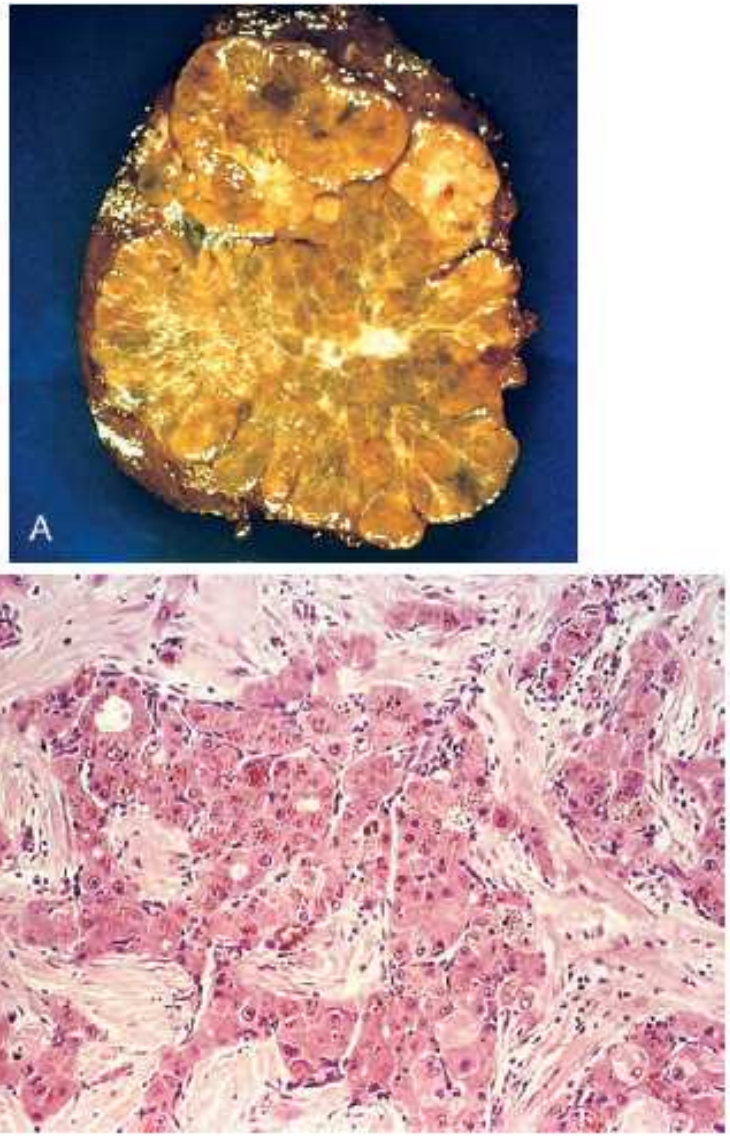


Figure 18-59 Fibrolamellar carcinoma. **A,** Resected specimen showing a well demarcated nodule. **B,** Microscopic view showing nests and cords of malignant-appearing, oncocytic hepatocytes separated by dense bundles of collagen.

Hepatocellular cancer

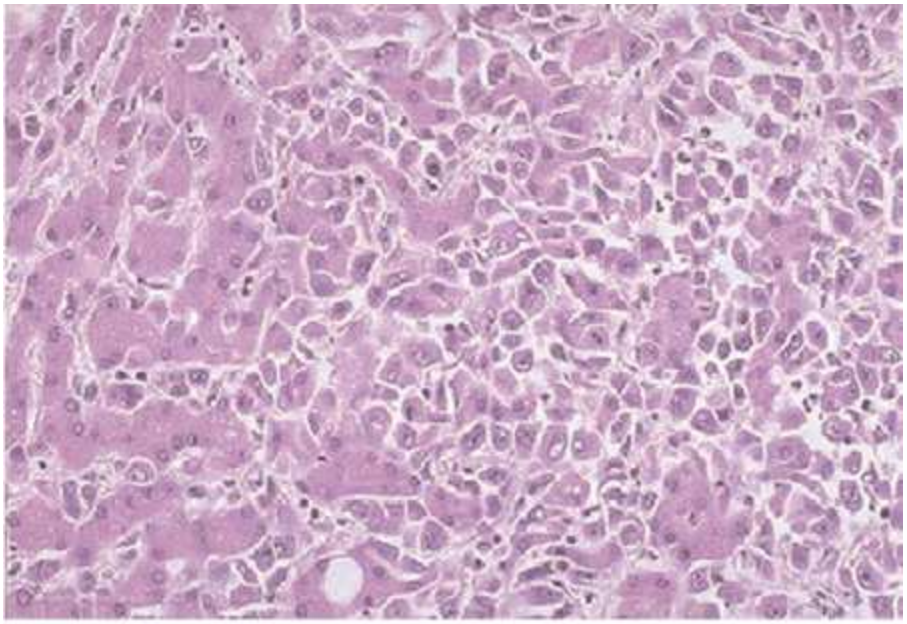


Fig. 15-10 Accessed 04/10/2010

Shown here is a moderately well differentiated neoplasm of polygonal cells in a trabecular patern. Rare nests and acini are identified.

Hepatocellular cancers may be univocal, multifocal, or diffuse.

There is a propensity to invade vascular structures.

The fibrolamellar variant is associated with marked fibrosis.

Prognosis and staging

- The Barcelona (BCLC) staging classification is the only classification that provides treatment recommendations for each of the assigned stages (early, intermediate, advanced, end-stage) based on best treatment options currently available.
- It has been validated in Europe, Asia, and the US.
- The BCLC is based on tumor size, number of tumor nodules, the presence of portal vein thrombosis, liver function (Child-Pugh score, portal hypertension, bilirubin level), performance status, and systemic symptoms.

Therapeutic approach

- Fewer than 20% are surgical candidates
- If detected at very early stage (single nodule <3cm) or early stage (single nodule <5cm or three nodules each <3cm), resection or ablation or liver transplant may be curative (>70% 5-year survival).
- No bilirubin abnormality
- Minimal portal hypertension
- Fever >38.6°C, microvascular invasion, hilar nodes are poor prognostic factors.
- Portal vein invasion excludes liver transplant.

Therapeutic approach

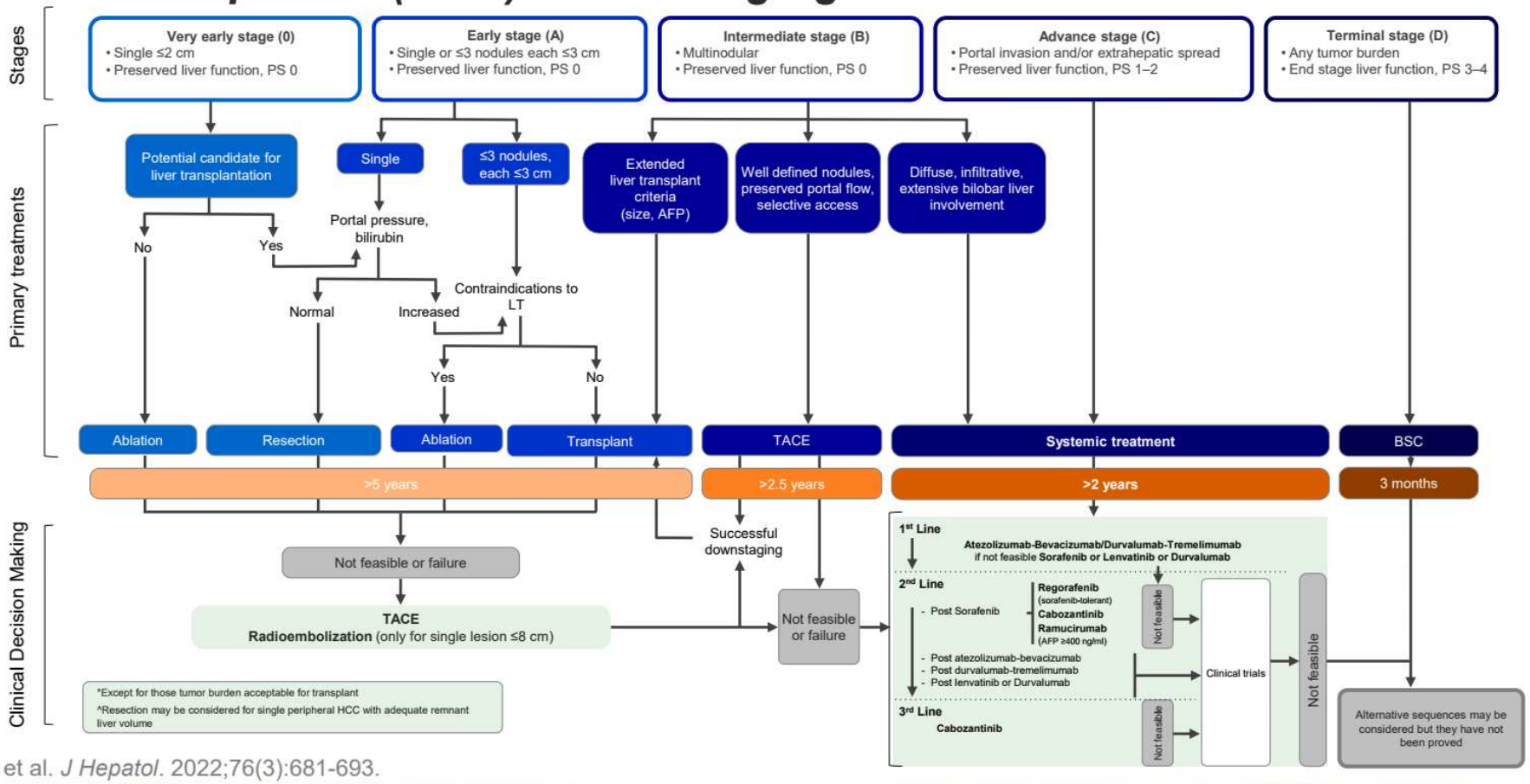
- Tumor is supplied by hepatic artery; liver, by portal vein.
- Multinodular lesions best treated with trans arterial chemoembolization
- 20 month median survival
- Hepatic arterial infusion chemotherapy with 5FU, doxorubicin, and mitomycin-C following gallbladder removal may lead to response in unresectable cases.
- ^{90}Yt also employed as alternative agent for hepatic arterial therapy.

Therapeutic approach

- If portal invasion, metastases, or nodal involvement, atezolizumab with bevacizumab is superior to single agent sorafenib or levantinib (tyrosine kinase inhibitors) as is durvalumab with tremelimumab
- Post-sorafenib, regorafenib, cabozantinib, or ramucirumab as second line therapy
- Must have failed sorafenib
- Ramucirumab effective if AFP>400 ng/ml
- Ipilimumab with pembromizulab as second line therapy
- Lung is most common site of metastasis

Potential Treatment Strategy

The Updated (2022) BCLC Staging and Treatment Guidance



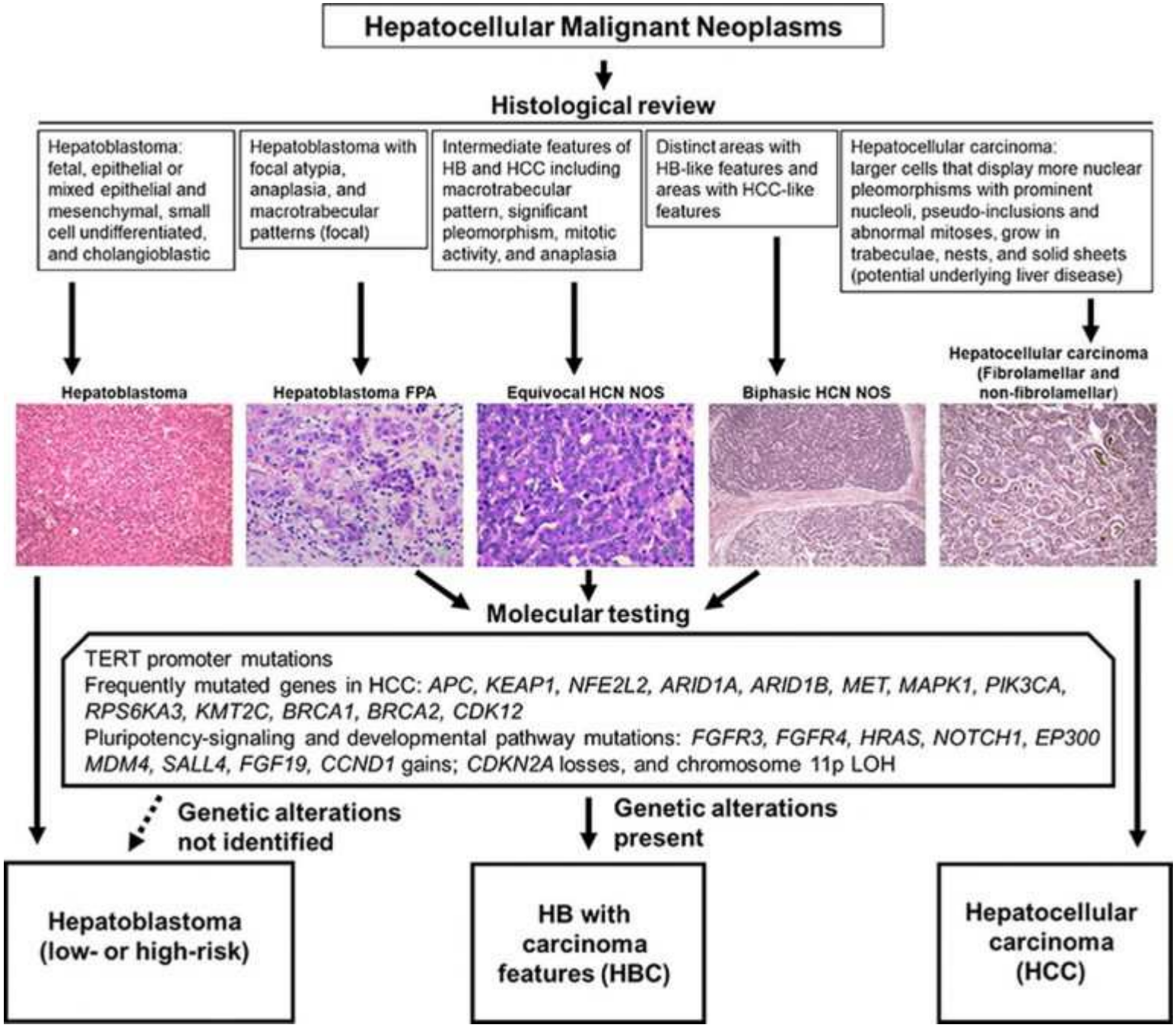
Reig M, et al. *J Hepatol*. 2022;76(3):681-693.

Hepatoblastoma

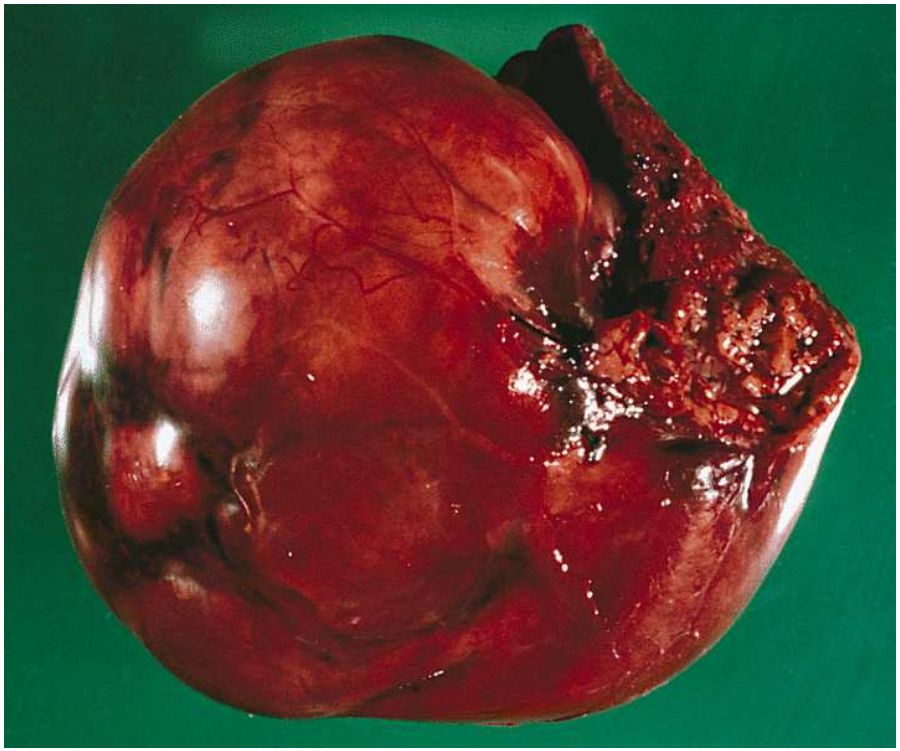
- Most common liver tumor in children.
- Peak age, 3 years.
- Hepatocellular cancer incidence varies little with age from birth to 19 years of age
- Single mass. 60-65% involve right lobe.
- No evidence of cirrhosis.
- Survival rate 70% after resection (25% if hepatocellular cancer).
- Elevated AFP.
- 11p15.5 allele loss (as in Beckwith-Wiedemann syndrome).
- 2% of hepatoblastoma patients have hemi-hypertrophy.

Hepatoblastoma

- Associated with familial adenomatous polyposis as the tumor has mutations in the Wnt/β-catenin gene.
- FOXG1, a regulator of TGF-β pathway, highly expressed in hepatoblastoma.
- Epithelial type composed of fetal or embryonal cells forming acini, tubules, or papillary structures recapitulating liver development.
- Foci of mesenchymal differentiation seen in mixed type.
- Advanced stage disease treated with cisplatin, vincristine, 5FU or cisplatin, doxorubicin chemotherapy followed by resection if possible.
- Resection associated with survival.


Hepatocellular Malignant Neoplasms
Histological review
Hepatoblastoma: fetal, epithelial or mixed epithelial and mesenchymal, small cell undifferentiated, and cholangioblastic
Hepatoblastoma with focal atypia, anaplasia, and macrotrabecular patterns (focal)
Intermediate features of HB and HCC including macrotrabecular pattern, significant pleomorphism, mitotic activity, and anaplasia
Distinct areas with HB-like features and areas with HCC-like features
Hepatocellular carcinoma: larger cells that display more nuclear pleomorphisms with prominent nucleoli, pseudo-inclusions and abnormal mitoses, grow in trabeculae, nests, and solid sheets (potential underlying liver disease)
Hepatoblastoma
Hepatoblastoma FPA
Equivocal HCN NOS
Biphasic HCN NOS
Hepatocellular carcinoma (Fibrolamellar and non-fibrolamellar)
Molecular testing
TERT promoter mutations
Frequently mutated genes in HCC: APC, KEAP1, NFE2L2, ARID1A, ARID1B, MET, MAPK1, PIK3CA, RPS6KA3, KMT2C, BRCA1, BRCA2, CDK12
Pluripotency-signaling and developmental pathway mutations: FGFR3, FGFR4, HRAS, NOTCH1, EP300 MDM4, SALL4, FGF19, CCND1 gains; CDKN2A losses, and chromosome 11p LOH
Genetic alterations not identified
Genetic alterations present
Hepatoblastoma (low- or high-risk)
HB with carcinoma features (HBC)
Hepatocellular carcinoma (HCC)

Hepatoblastoma

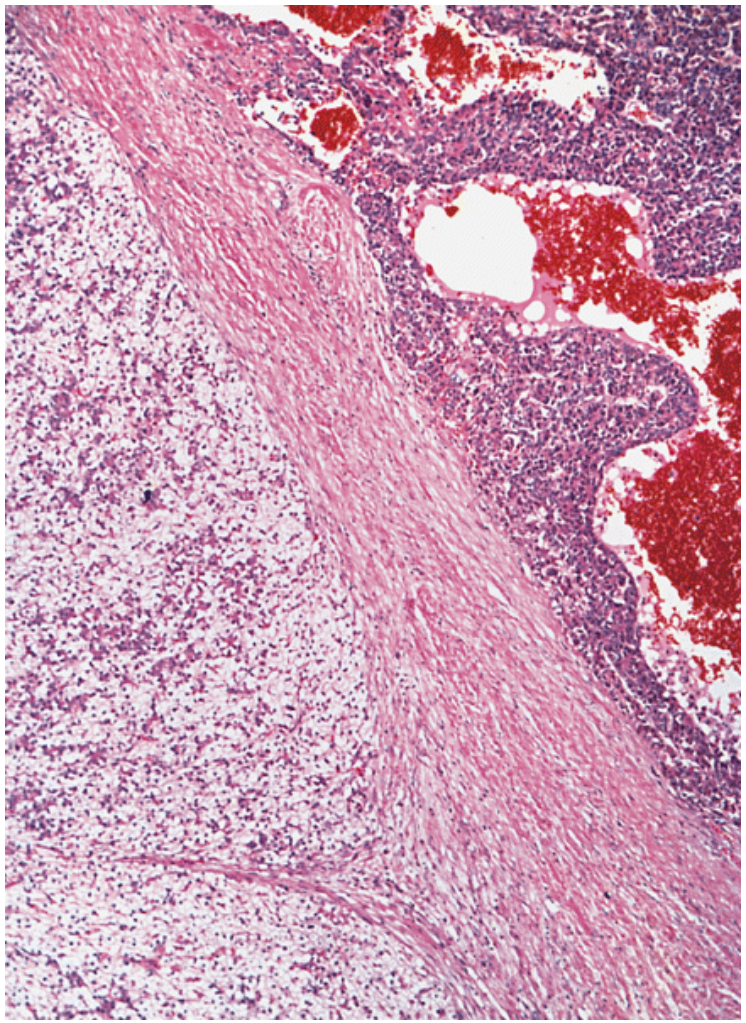


The external surface shows a bulging, red-tan mass resected from the right lobe, which displays an intact smooth capsule traversed by many blood vessels.

Fig. 6-1

Ishak, KG, Goodman, ZD, Stocker, JT. “Tumors of the liver and intrahepatic bile ducts.” Atlas of Tumor Pathology, Third Series, Fascicle 31. Armed Forces Institute of Pathology, Washington, D.C. 2001.

Hepatoblastoma

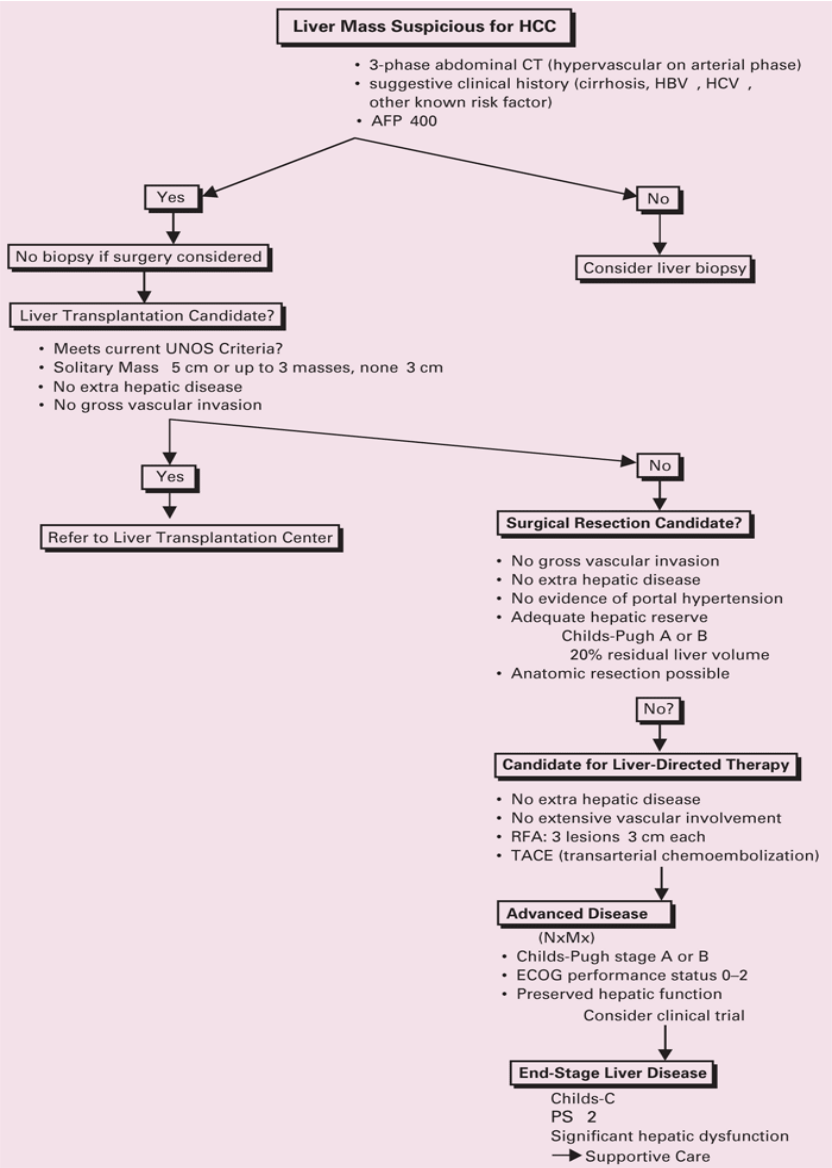


Fetal epithelial cells with a high cytoplasmic lipid concentration (bottom left) are separated by a band of fibrous connective tissue from a vascular mass of more "immature" appearing embryonal cells (top right).

Fig. 6-14

Ishak, KG, Goodman, ZD, Stocker, JT. “Tumors of the liver and intrahepatic bile ducts.” Atlas of Tumor Pathology, Third Series, Fascicle 31. Armed Forces Institute of Pathology, Washington, D.C. 2001.

Strategy



Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com

Fig. 15-13 Accessed 04/10/2010

Angiosarcoma

- Associated with 25 - 42% associated with exposure to androgen steroids, arsenic, Thorotrast, vinyl chloride.
- Patients with exposure to Thorotrast or vinyl chloride may have synchronous cholangiocarcinoma or hepatocellular carcinoma
- Cases with above known causes usually have latent period of 20 - 35 years, are accompanied by fibrosis or cirrhosis, have precursor conditions of hypertrophy and atypia of hepatocytes and sinusoidal lining cells but are histologically similar to idiopathic cases

Angiosarcoma

- 75% men, usually age 50+ years; rare in children
- Nonoperative biopsy may cause severe bleeding and death
- Most patients die within 6 months from hepatic failure or intra-abdominal bleeding
- Metastasizes widely, often to lung (vinyl chloride cases usually don't have distant metastases)

Angiosarcoma

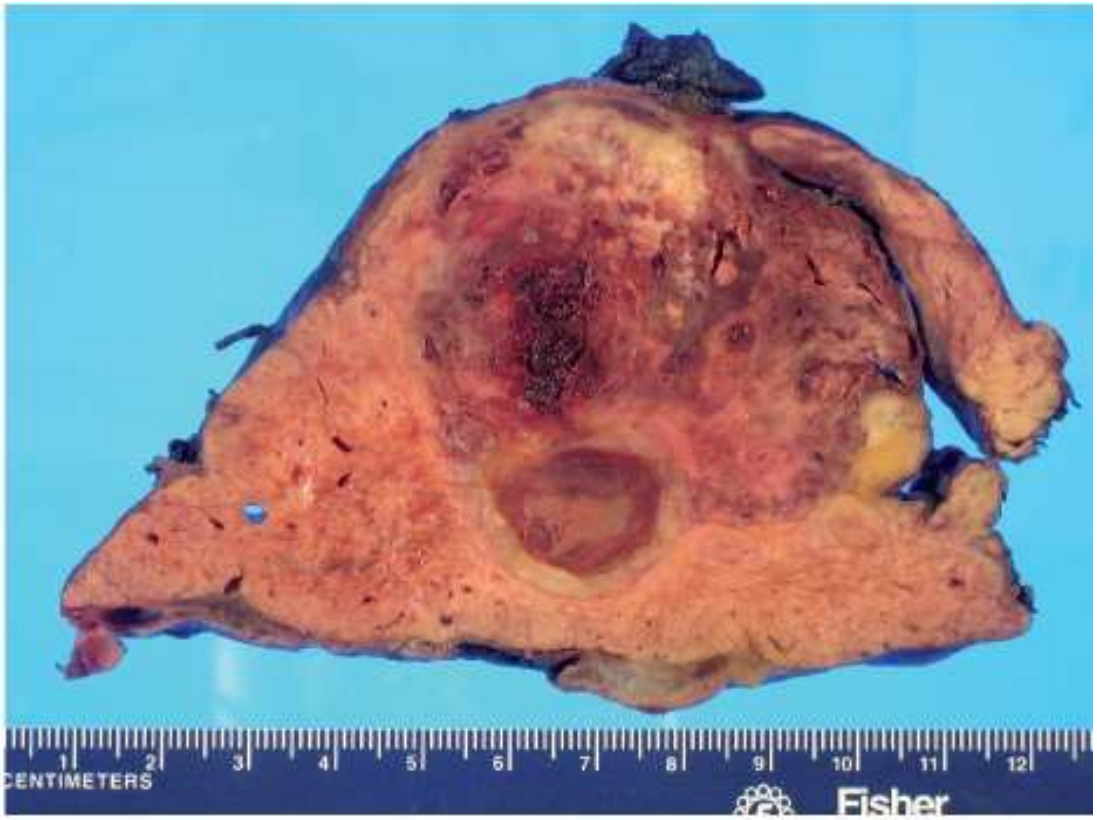
- Multicentric, involves right and left lobes
- Diffusely infiltrative, hemorrhagic and gray white solid nodules with blood filled cavities
- Thorotrast associated tumors have subcapsular hepatic and splenic deposits of yellow chalky material

Angiosarcoma

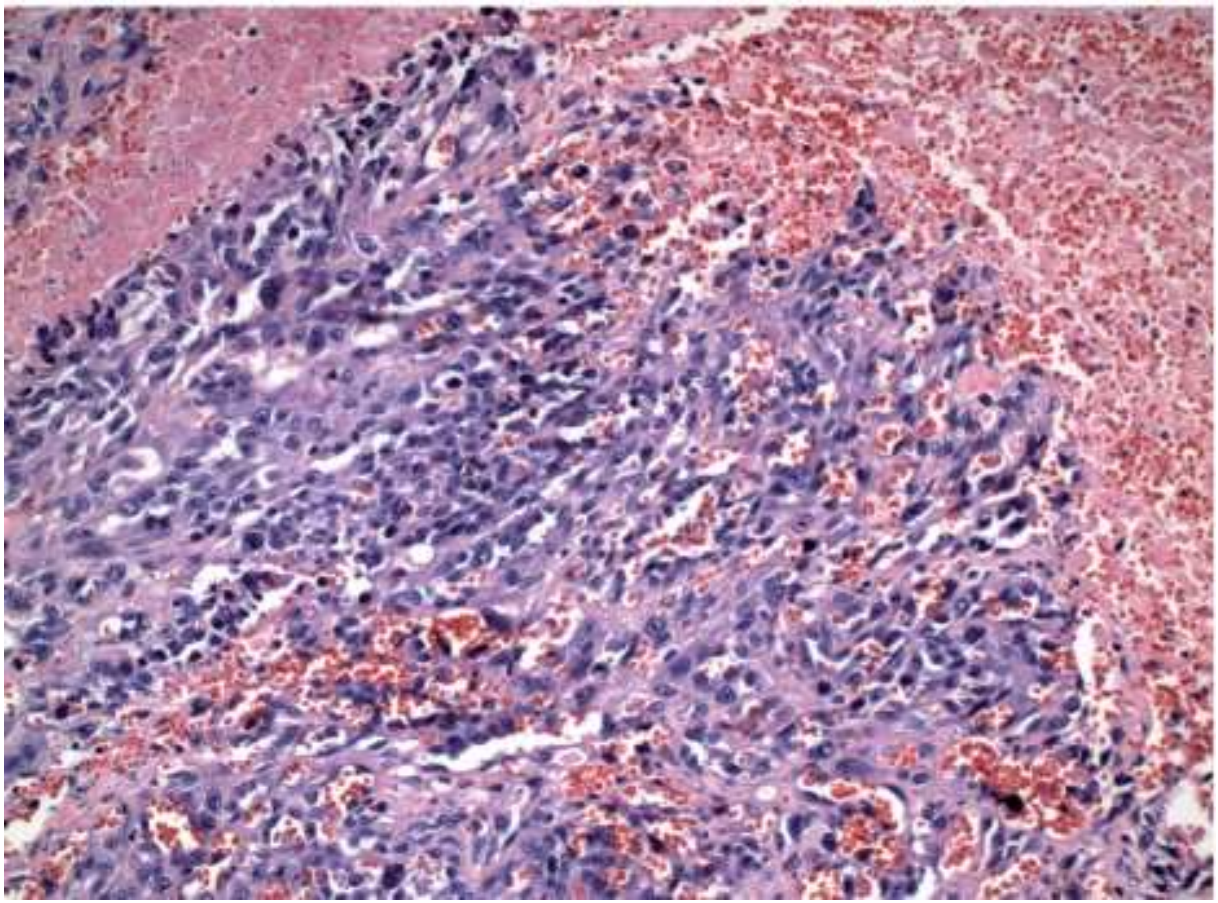
- Tumor composed of infiltrative, freely anastomosing vascular channels
- Tumor cells grow along sinusoids adjacent to hepatic cords
- Tumor cells have abundant, pale eosinophilic cytoplasm, poorly defined cell borders, are usually pleomorphic with hyperchromatic nuclei but may be only mildly atypical

Angiosarcoma

- Also variably prominent nucleoli, blood filled cavities present are lined by tumor cells that may be papillary
- 75% have vascular invasion of portal or hepatic vein branches; frequent mitotic activity



Cioffi-Pretti, JL, et al.,
Rare Tumors. 2009 Dec 28; 1(2): e33. doi: 10.4081/rt.2009.e33
Accessed 04/20/2021



Cioffi-Pretti, JL, et al.,
Rare Tumors. 2009 Dec 28; 1(2): e33. doi:
10.4081/rt.2009.e33
Accessed 04/20/2021

Cholangiocarcinoma

- 10% of all hepatic cancers
- Second most common cancer of hepatobiliary tree
- 50-70 years of age
- Associated with:
- Fluke infection (Asia)
- Primary sclerosing cholangitis
- HCV infection
- Caroli's disease (congenital fibropolycystic disease of the biliary system).

Cholangiocarcinoma

- Peritoneal seeding is uncommon.
- Cholangiocarcinoma is subdivided into:
- Proximal extrahepatic (perihilar or Klatskin tumor, 50-60%)
- At the hilum (bifurcation of right and left ducts).
- Distal extrahepatic (20-25%)
- Intrahepatic (peripheral, 20-25%).
- 10% exclusively intrahepatic

Cholangiocarcinoma

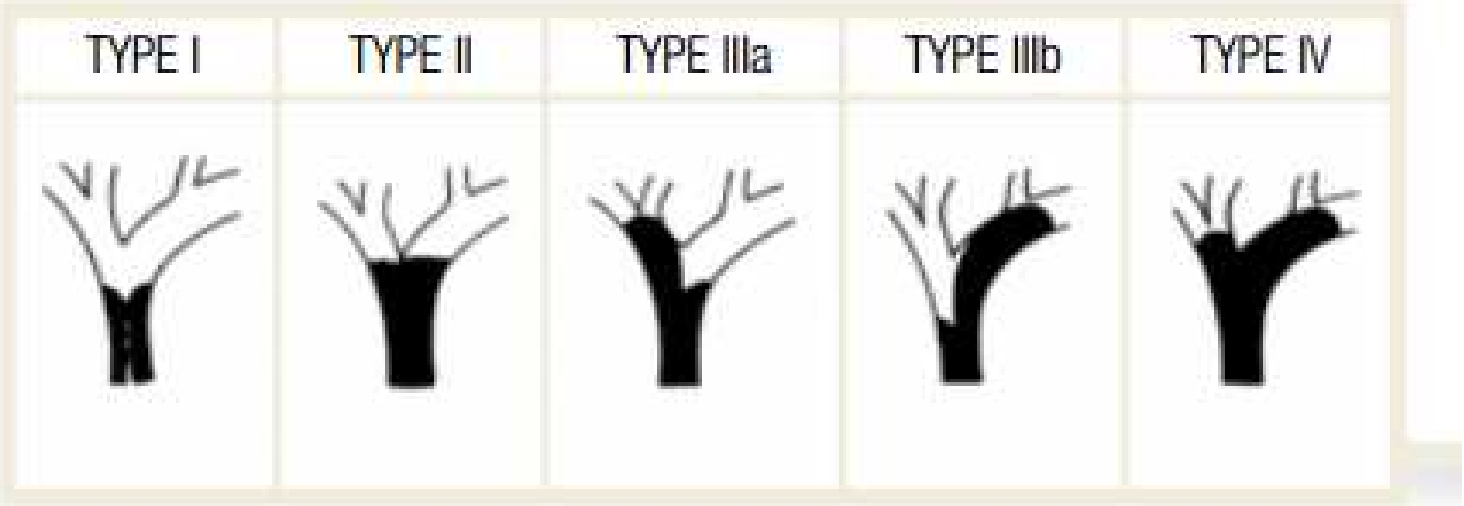
- Extrahepatic origin
- Tumors appear as firm, gray nodules within the bile duct wall
- Some may be diffusely infiltrative lesions
- Others are papillary, polypoid lesions.
- Intrahepatic origin
- Occur in the non-cirrhotic liver and may track along the intrahepatic portal tract system creating a branching tumor within a portion of the liver
- Cholangiocarcinomas do not make bile, but they do make mucin

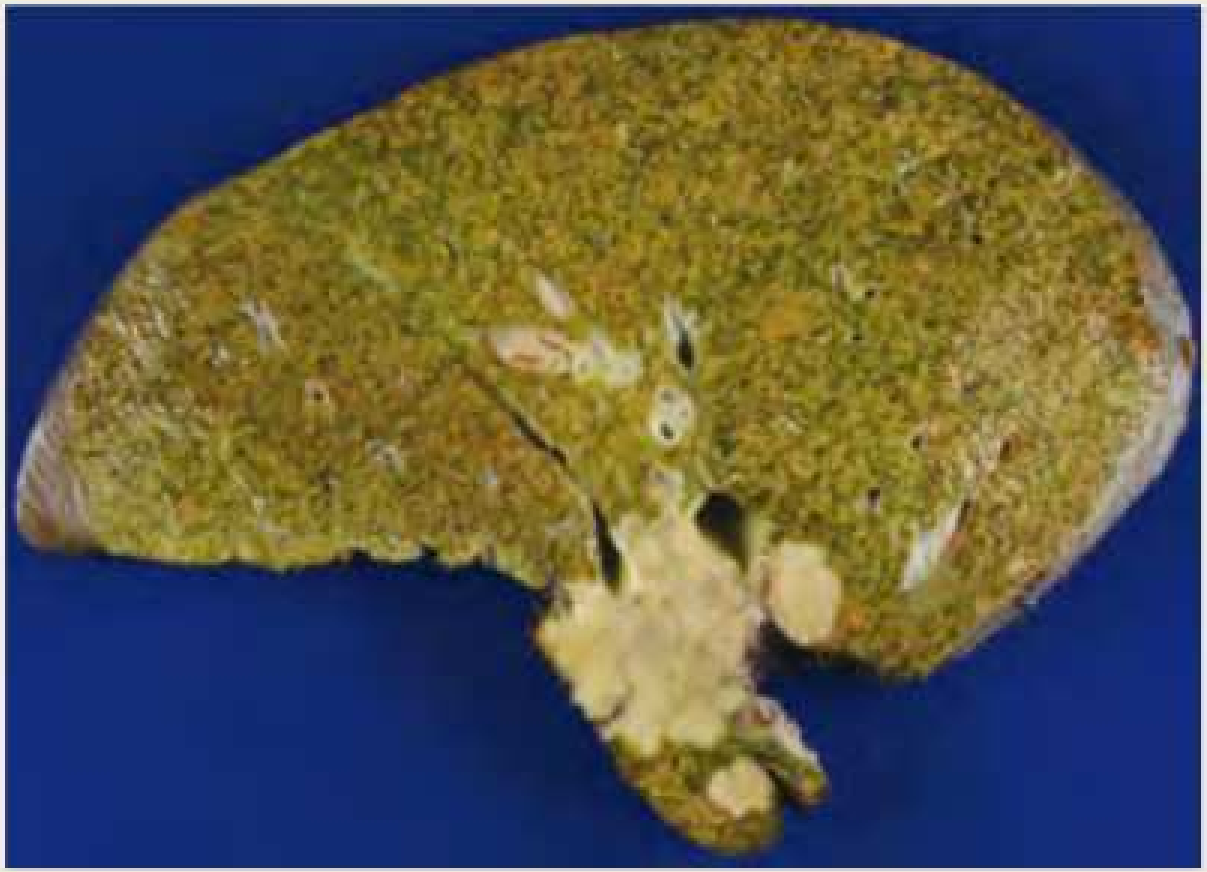
Cholangiocarcinoma

- IL-6 overexpression and AKT activation
- IL-6 drives JAK/STAT signaling
- The anti-apoptotic protein MCL-1 is increased.
- KRAS and TP53 mutations are common
- COX2, ERBB2, C-MET expression increased.
- Amplification of EFGR and diminished function of p16/ink4A have also been noted.
- FGFR2 mutation at 10q26.13 gives rise to a gene fusion product
- Targeted by futibatinimib
- KMT2C mutation at 7q36.1 common in Asians

Cholangiocarcinoma: classification

Bismuth–Corlette classification





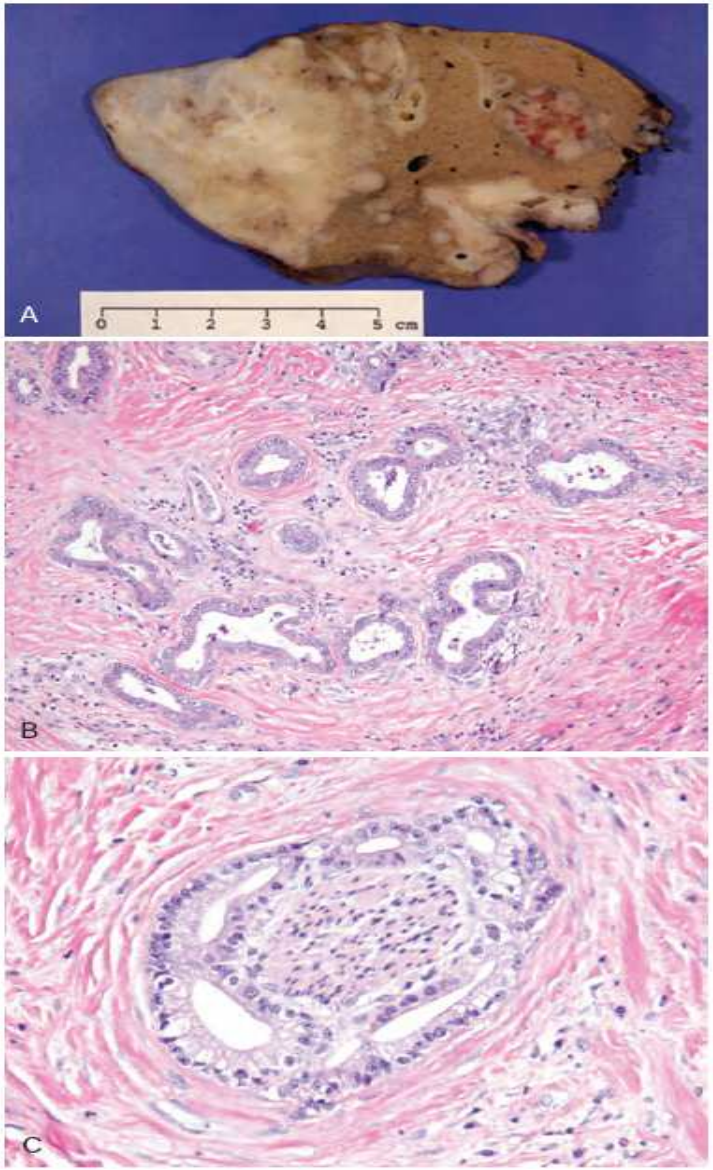
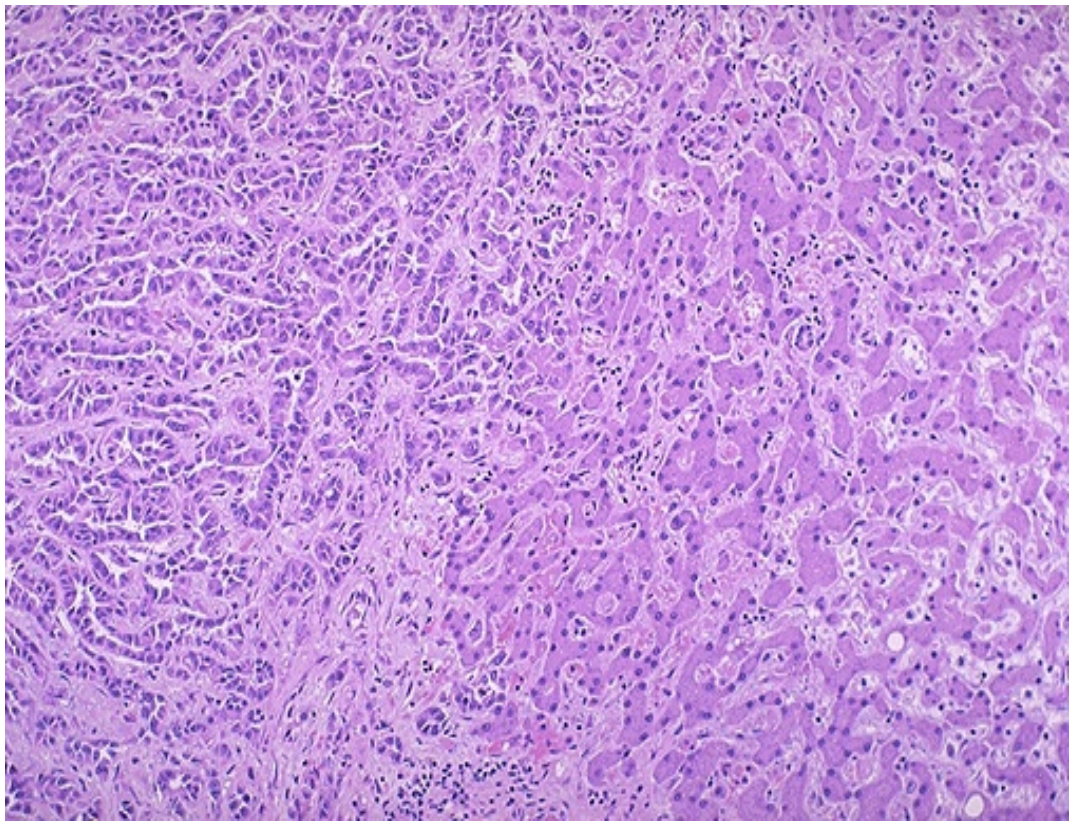


Figure 18-60 Cholangiocarcinoma. **A,** Multifocal cholangiocarcinoma in a liver from a patient with infestation by the liver fluke *Clonorchis sinensis*. **B,** Invasive malignant glands in a reactive, sclerotic stroma. **C,** Perineural invasion by malignant glands, forming a wreathlike pattern around the central, trapped nerve. (**A,** Courtesy Dr. Wilson M.S. Tsui, Caritas Medical Centre, Hong Kong.)

Cholangiocarcinoma



The carcinoma at the left has a glandular appearance that is most consistent with a cholangiocarcinoma.

There is a disorderly arrangement of ducts lined by neoplastic biliary epithelium.

A liver cancer may have both hepatocellular as well as cholangiolar differentiation.

https://webpath.med.utah.edu/LIVEHTML/LIVER032.html
Accessed 12/10/2019

BILARY TRACT AND GALLBLADDER

Arterial supply to pancreas

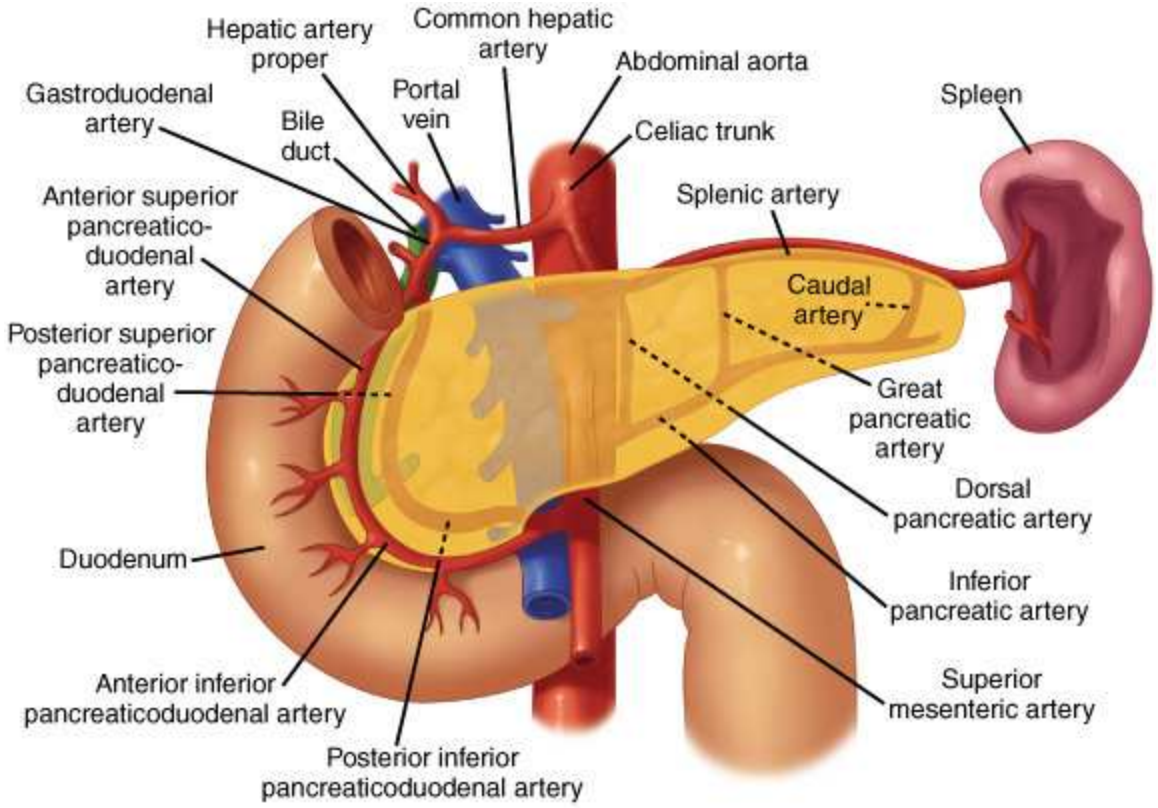
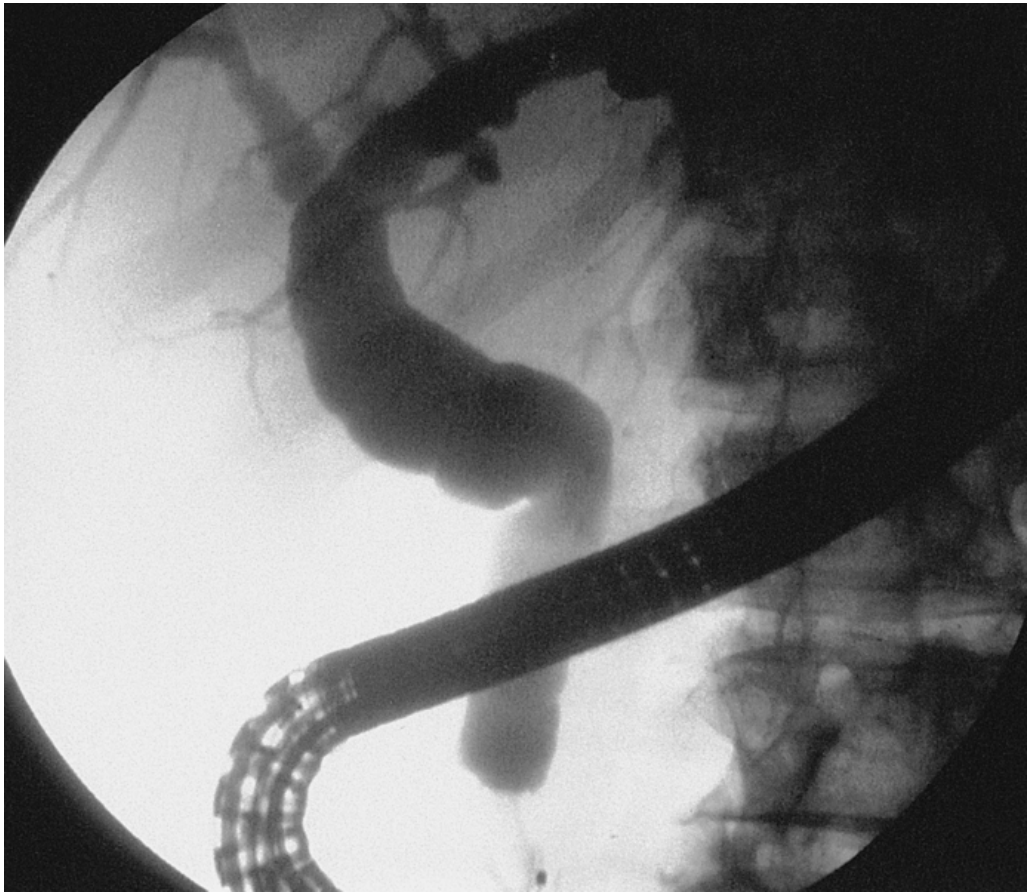


Fig. 33-4 Accessed 02/01/2010

Biliary tract cancer

- Generally present with pain and right upper quadrant mass.
- Bile duct lesions generally present with obstruction
- Polyps >1cm diameter have the greatest malignant potential.
- MRI-cholangiopancreatography is the optimal imaging procedure to outline local anatomy.

Bile duct obstruction



The ERCP reveals a tight, irregular, distal common bile duct stricture caused by a well-differentiated adenocarcinoma.

Fig. 12-4

Albores-Saavedra, J, Henson DE, Klimstra ,DS, “Tumors of the extrahepatic bile ducts, and ampulla of Vater.” Atlas of Tumor Pathology, Third Series, Fascicle 27. Armed Forces Institute of Pathology, Washington, D.C. 2000.

Periampullary neoplasms

- Adenomas are <10% or periampullary neoplasms
- Duodenal adenoma only distinguished by site
- Generally occur in older individuals
- Usually asymptomatic but can cause gastric outlet obstruction or bleeding and rarely acute pancreatitis, biliary obstruction or intussusception
- Present as polypoid or exophytic mass
- May be seen with familial adenomatous polyposis

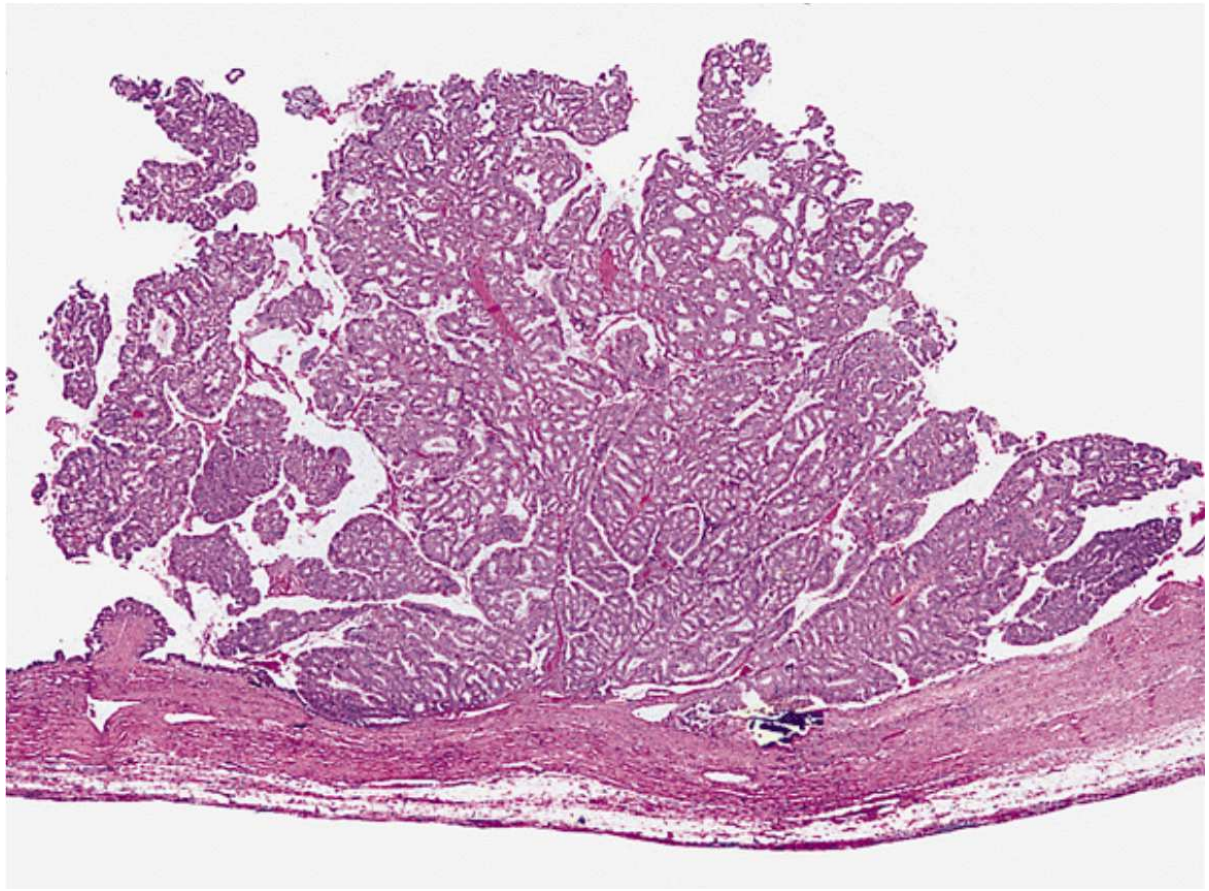
Periampullary neoplasms

- Microscopically:
- Tubular or villous or mixed tubular/villous adenomas as in colon
- Paneth cells, endocrine cells, goblet cells noted
- May have pancreatobiliary epithelium
- BRAF mutations, p53 alterations and DNA mismatch repair abnormalities are rare
- KRAS and APC mutations are more common, both in sporadic cases and in those from patients with familial adenomatous polyposis.

Periampullary neoplasms

- Resection may be curative in early or relatively confined lesions
- If not confined, may require pancreatoduodenectomy

Pyloric gland adenoma

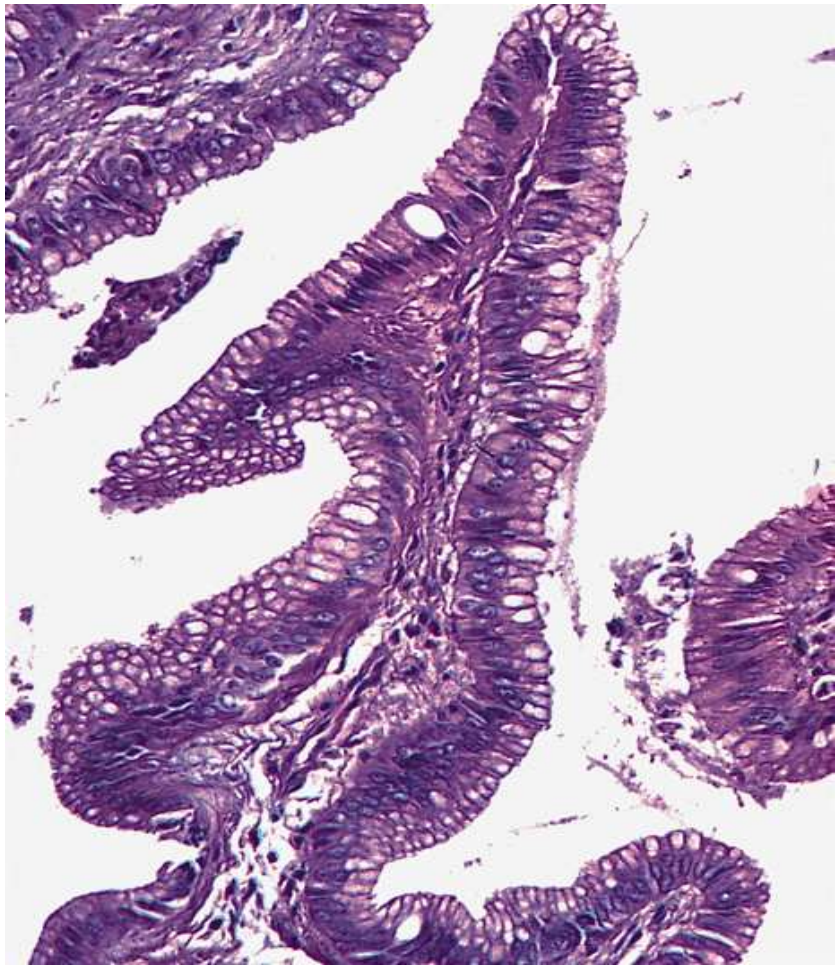


Low- power view of a sessile pyloric gland adenoma containing some dilated glands.

Fig. 3-5L

Albores-Saavedra, J, Henson DE, Klimstra ,DS, “Tumors of the extrahepatic bile ducts, and ampulla of Vater.” Atlas of Tumor Pathology, Third Series, Fascicle 27. Armed Forces Institute of Pathology, Washington, D.C. 2000.

Biliary adenoma



A papillary adenoma is composed of fibrovascular stalks that extend outward into the lumen of the gallbladder. They are lined by tall, columnar, mucus- secreting cells.

Fig. 3-19

Albores-Saavedra, J, Henson DE, Klimstra ,DS, “Tumors of the extrahepatic bile ducts, and ampulla of Vater.” Atlas of Tumor Pathology, Third Series, Fascicle 27. Armed Forces Institute of Pathology, Washington, D.C. 2000.

Gallbladder adenocarcinoma

- Generally present with pain and right upper quadrant mass.
- 3:1 women
- 50-60 years of age
- Prevalent among Native American populations (particularly in Southwest), Bolivia, Chile, and in North India
- Primarily affects the fundus (60%), body (30%) or neck (10%) of gallbladder

Gallbladder adenocarcinoma

- Cholelithiasis, Salmonella, E. Coli, and H. pylori infections predispose.
- Porcelain gallbladder can be associated with cancer in 20% of patients.

Gallbladder adenocarcinoma

- Up to 50% are detected incidentally in routine cholecystectomy specimens due to absence of gross abnormalities
- Peritoneal seeding is uncommon.
- Noninvasive papillary carcinomas, regardless of size and differentiation, do not metastasize
- Invasive papillary carcinomas have the most favorable prognosis
- Aggressive cancer, with an overall 5 year survival rate of < 10%

Gallbladder adenocarcinoma

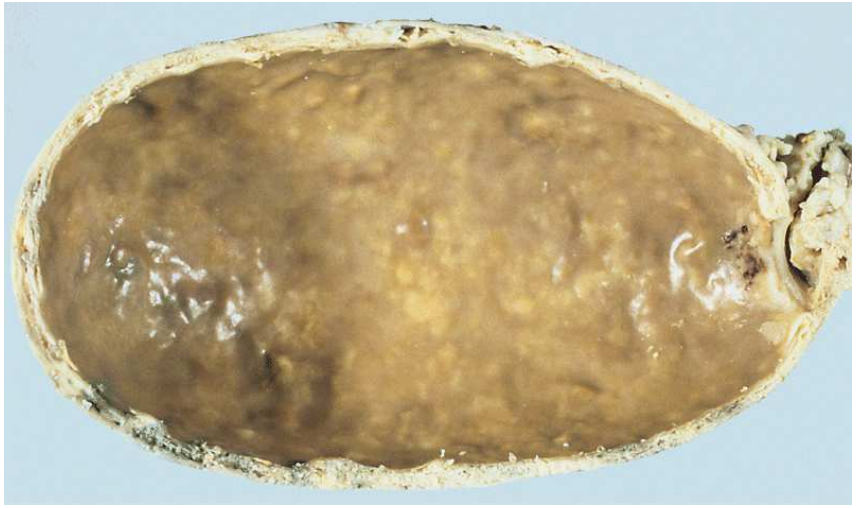
- Histologic types:
- (1) Biliary type adenocarcinoma
- 75% of cases:
- (2) Intestinal type adenocarcinoma:
- (3) Mucinous carcinoma:
- Comprised of > 50% extracellular mucin
- (4) Clear cell carcinoma:
- Sheets of clear cells in an alveolar arrangement separated by blood vessels

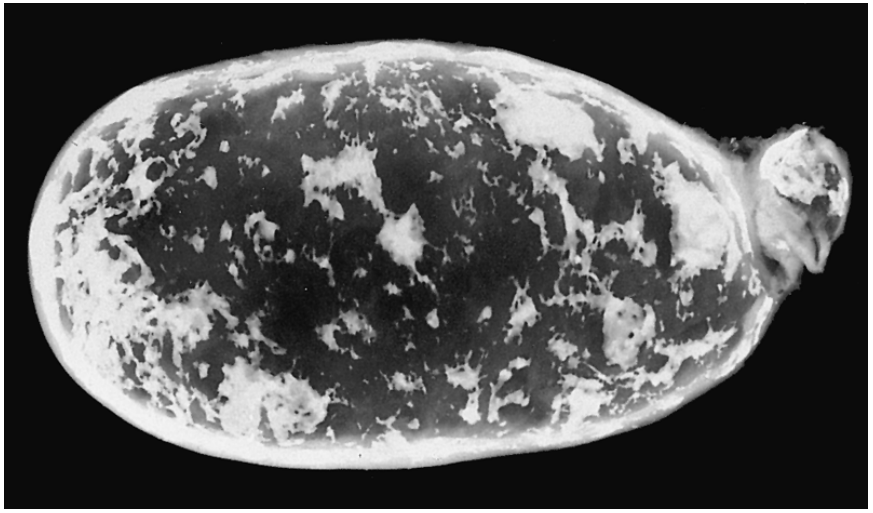
Gallbladder adenocarcinoma

- (5) Signet ring cell carcinoma:
- Signet ring cells are the predominant or exclusive component
- (6) Hepatoid carcinoma:
- (7) Sarcomatoid carcinoma (carcinosarcoma)

- 30-60% ERBB2 over expressed

Porcelain gallbladder



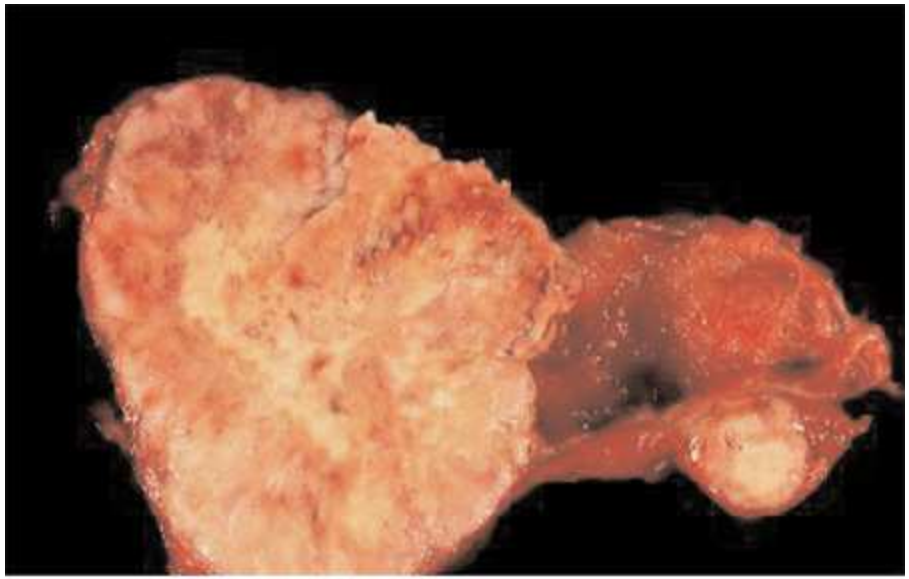


The wall of this large distended gallbladder is rigid and calcified. A stone found in the neck had been previously removed.

Figs. 4-2 and 4-3

Albores-Saavedra, J, Henson DE, Klimstra ,DS, “Tumors of the extrahepatic bile ducts, and ampulla of Vater.” Atlas of Tumor Pathology, Third Series, Fascicle 27. Armed Forces Institute of Pathology, Washington, D.C. 2000.

Gallbladder carcinoma

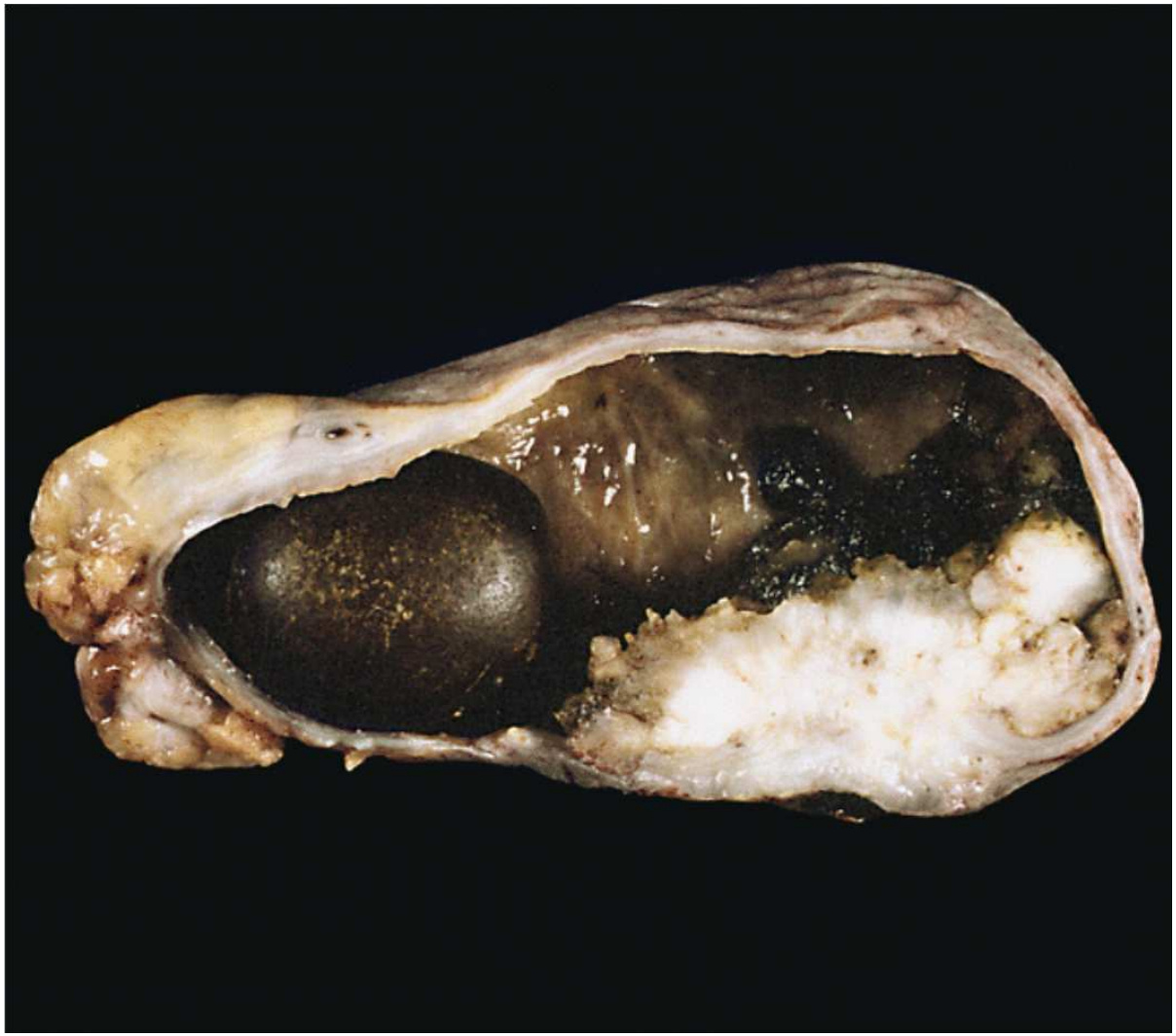


Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com

Gallbladder lumen is filled with tumor.

Fig.15-12 Accessed 04/10/2010

Adenocarcinoma

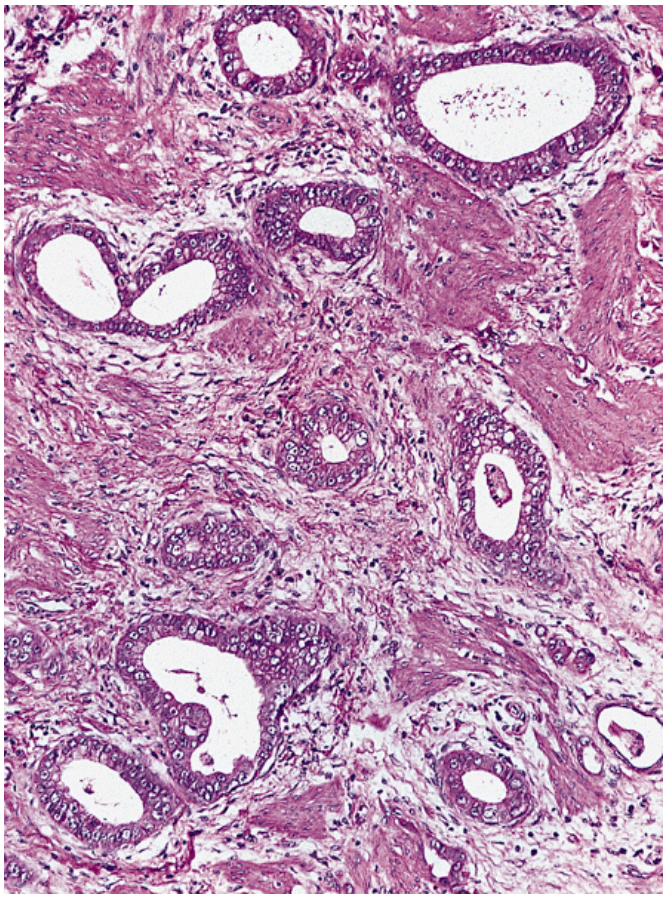


Gallbladder excised for cholelithiasis. A small infiltrating carcinoma was found in a thickened area of the fundus. Early changes may be mistaken for cholecystitis.

Fig. 6-3

Albores-Saavedra, J, Henson DE, Klimstra ,DS, “Tumors of the extrahepatic bile ducts, and ampulla of Vater.” Atlas of Tumor Pathology, Third Series, Fascicle 27. Armed Forces Institute of Pathology, Washington, D.C. 2000.

Adenocarcinoma



A well-differentiated adenocarcinoma is composed of variable sized glands that infiltrate the muscular wall of the gallbladder.

Fig. 6-9

Albores-Saavedra, J, Henson DE, Klimstra ,DS, “Tumors of the extrahepatic bile ducts, and ampulla of Vater.” Atlas of Tumor Pathology, Third Series, Fascicle 27. Armed Forces Institute of Pathology, Washington, D.C. 2000.

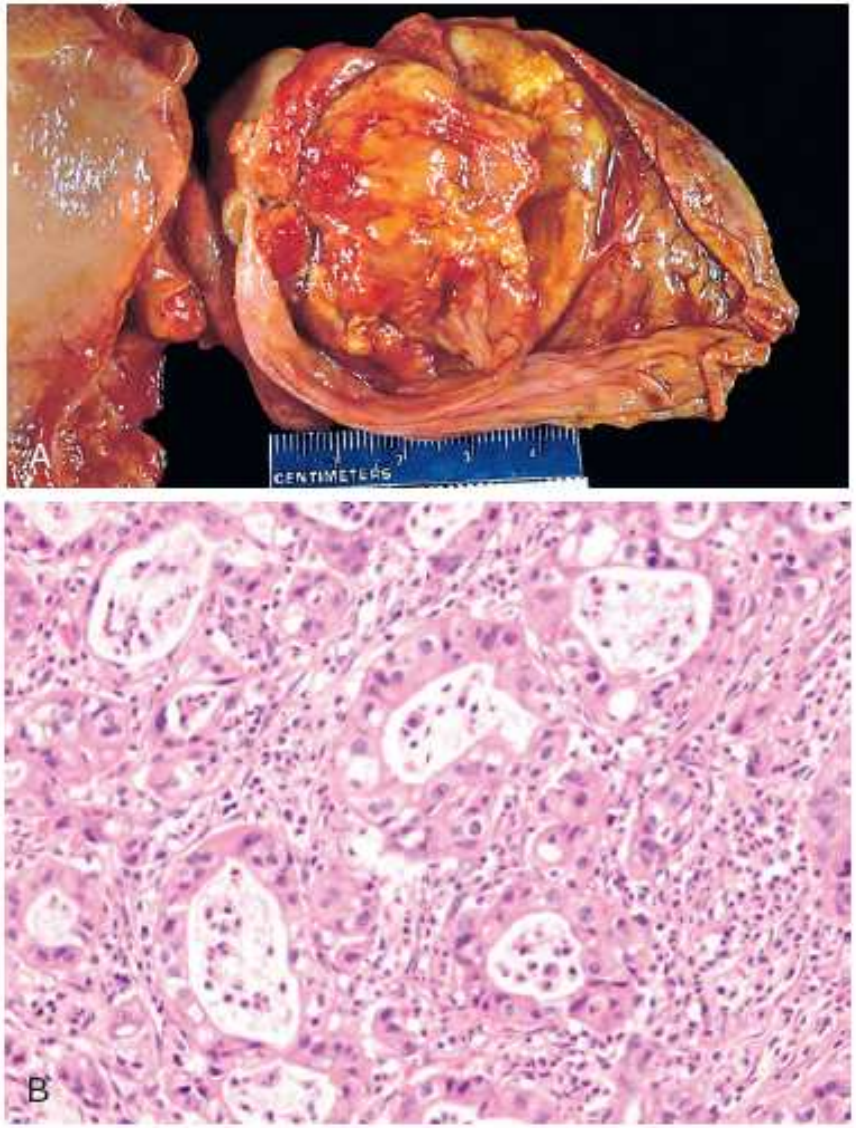


Figure 18-65 Gallbladder adenocarcinoma. **A,** The opened gallbladder contains a large, exophytic tumor that virtually fills the lumen. **B,** Malignant glands are seen infiltrating a densely fibrotic gallbladder wall.

Treatment of gallbladder adenocarcinoma

- Hilar / portal lymphadenectomy, plus resection of hepatic bed and the common bile duct to achieve negative margins, is necessary for tumors that extend into a muscle or beyond (pT1b - pT3)
- Recurrence common
- High histologic grade (poor differentiation) and vascular invasion have adverse outcomes
- Rokitansky-Aschoff sinus involvement by carcinoma and cystic duct margin status are suspected predictors of progression

Treatment of gallbladder adenocarcinoma

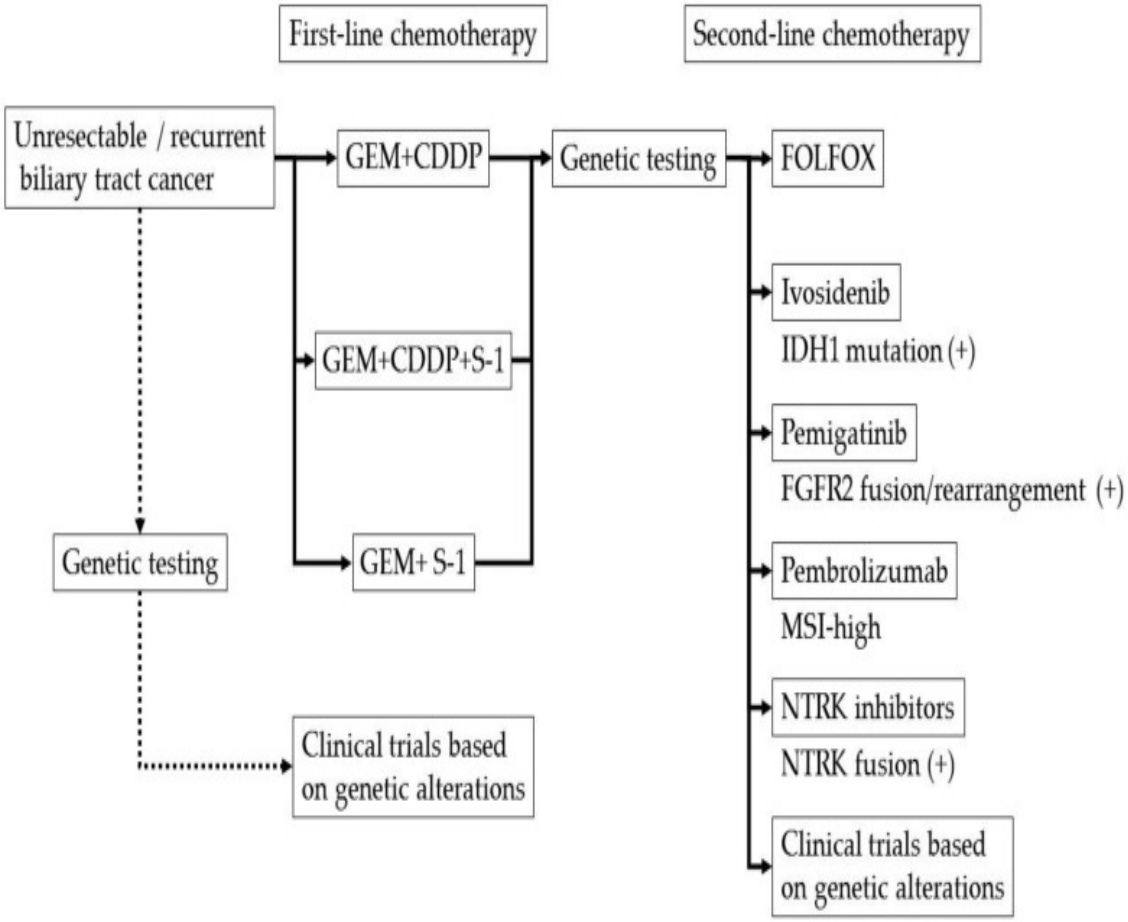
- 20% above bifurcation; else, evenly divided between hepatic and common bile duct.
- Chemotherapy or radiation for metastatic tumors

Treatment approach for biliary tract cancer

- Peritoneal seeding is uncommon
- <30% considered for curative resection
- Intrahepatic disease is treated with resection of involved liver.
- Hilar disease below or reaching the confluence of right and left hepatic ducts is treated with en bloc resection of extrahepatic bile ducts, gallbladder, regional lymph nodes, and a Roux-en-Y hepaticojejunostomy, as well as resection of segments V and IVB of the liver is performed.

Treatment approach for biliary tract cancer

- Tumors occluding the common duct may be stented.
- Else, extended right and left hepatectomy is added to the resection.
- Distal disease is treated with pancreaticoduodenectomy
- Improved results with cisplatin and gemcitabine chemotherapy.


First-line chemotherapy
Second-line chemotherapy
Unresectable / recurrent biliary tract cancer
GEM+CDDP
GEM+CDDP+S-1
GEM+ S-1
Genetic testing
Genetic testing
FOLFOX
Ivosidenib
IDH1 mutation (+)
Pemigatinib
FGFR2 fusion/rearrangement (+)
Pembrolizumab
MSI-high
NTRK inhibitors
NTRK fusion (+)
Clinical trials based on genetic alterations
Clinical trials based on genetic alterations