

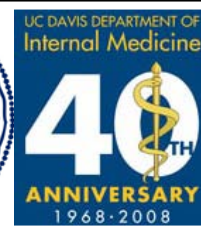
CHOLANGIOCARCINOMA AND PRIMARY SCLEROSING CHOLANGITIS

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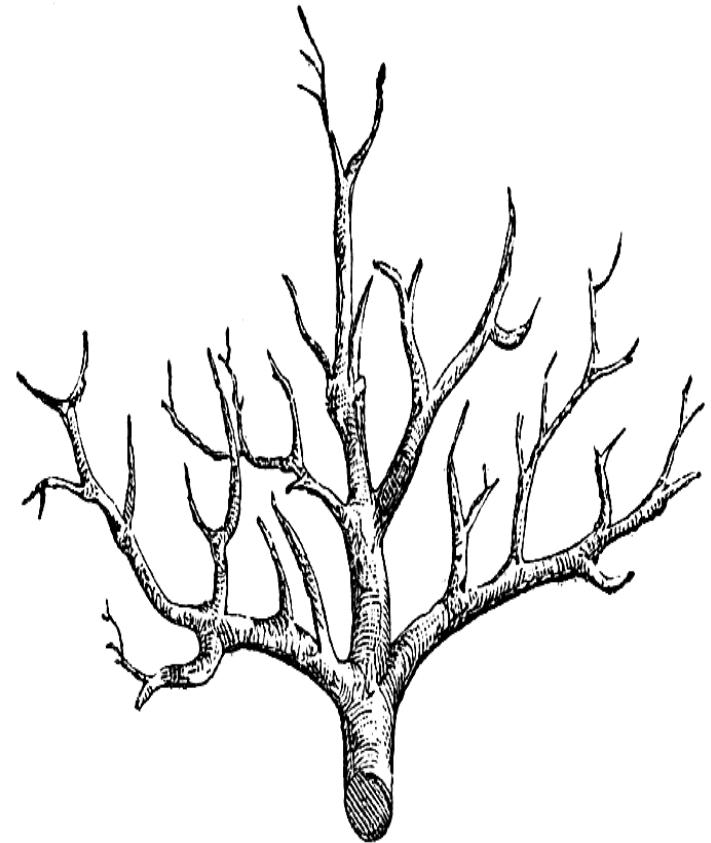
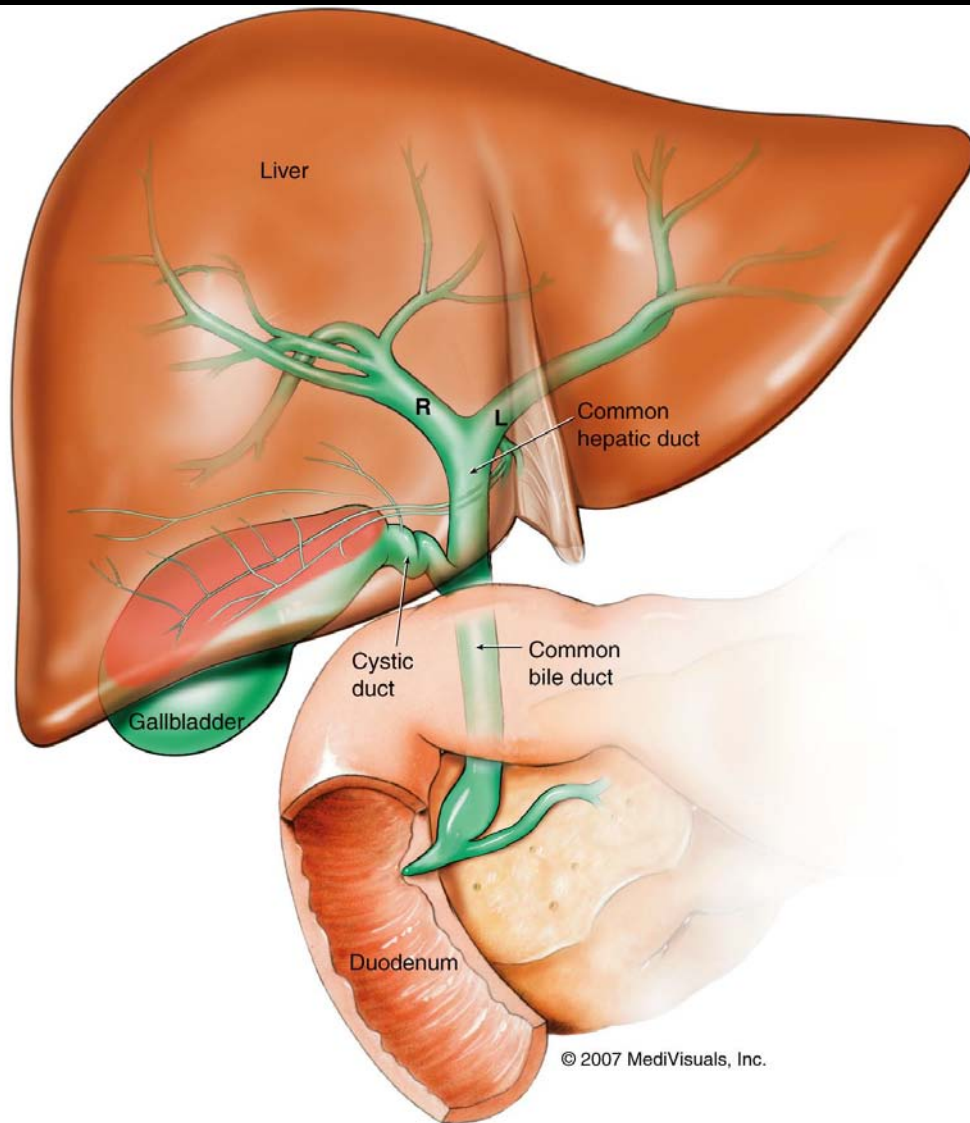
CHOLANGIOCARCINOMA (CCA)

ABERRANT PROLIFERATION OF BILE DUCT
EPITHELIAL CELLS

CCA is the second most common liver cancer

It may arise at any level of the biliary tree

BILIARY TREE



ANATOMY (I)

Intrahepatic tumors (25-50%)

Extrahepatic tumors (50-75%)

Hilar tumors (Klatzkin)

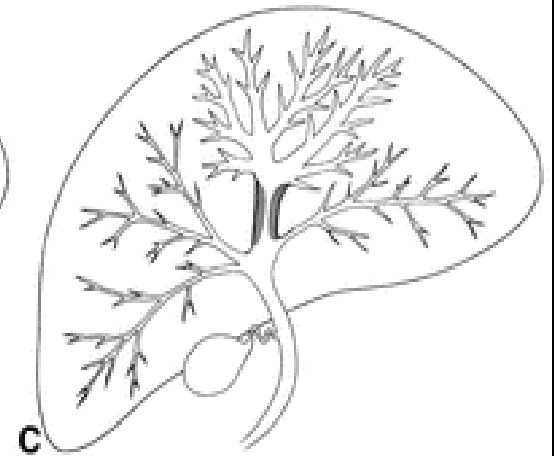
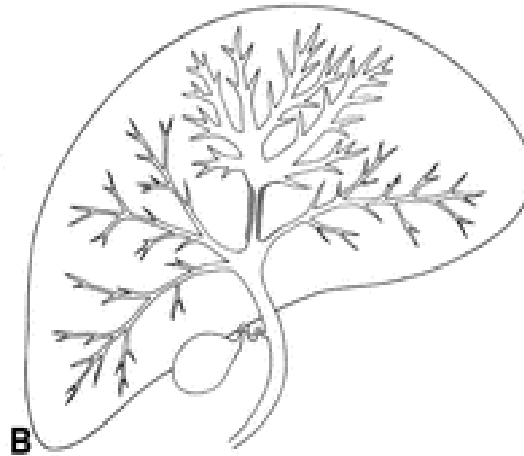
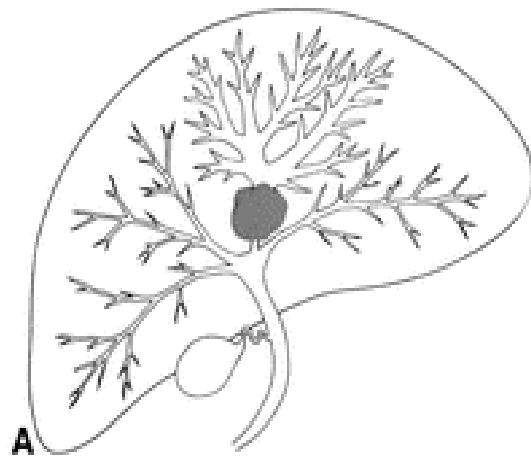
ANATOMY (II)

Mass forming

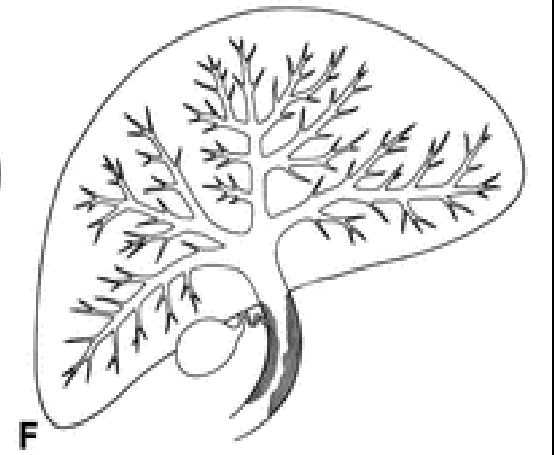
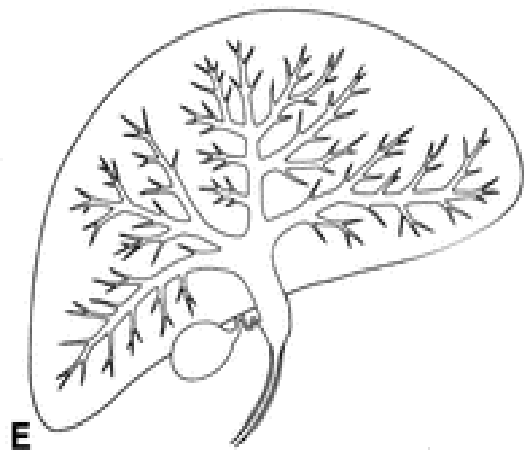
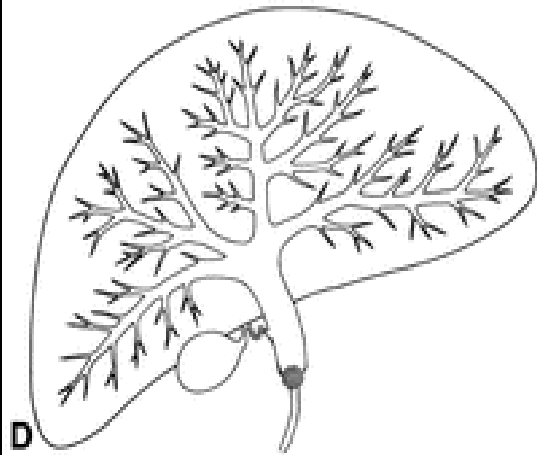
Periductal infiltration

Intraductal growing

INTRA-Hepatic



EXTRA-Hepatic

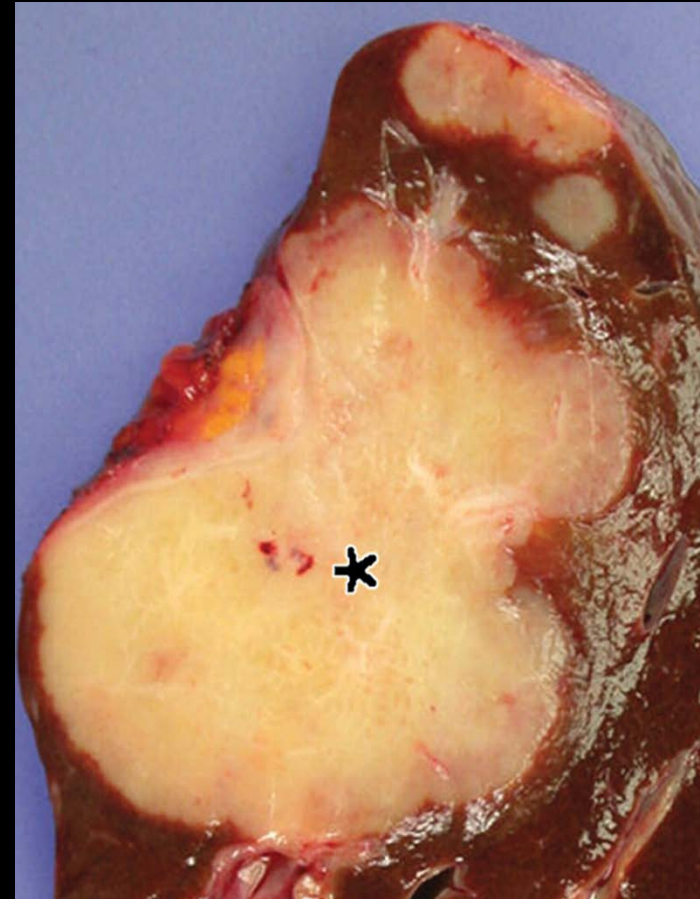


HISTOLOGY (I)

MACROSCOPIC ASPECT

The mass appears pale in color, usually yellow or white

The consistence is solid, dense and the tumor seems granular at touch due to the high amount of collagen

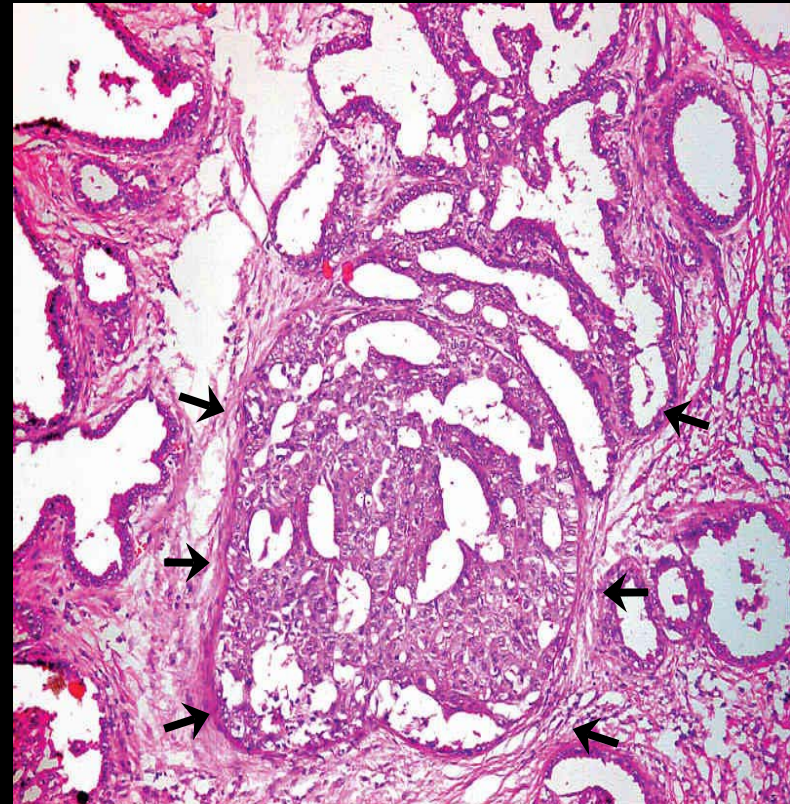


HISTOLOGY (II)

MICROSCOPIC FEATURES

Widespread spectrum:

From well defined tubular and glandular structures covered by cubical epithelial cells to unformed and chaotic mass with undifferentiated cells.



It can synthesize a capsule but frequently presents an aggressive vascular, subepithelial and lymphatic invasion.

CLINICAL PRESENTATION (I)

INTRAHEPATIC TUMORS may present with:

- Fatigue
- Malaise
- Abdominal fullness or discomfort
- Right upper abdominal mass
- Weight loss

CLINICAL PRESENTATION (II)

EXTRAHEPATIC TUMORS

PAINLESS OR MILD PAIN JAUNDICE (> 90%)

with accompanying:

- clay colored stools
- pruritus
- dark urine
- abdominal pain
- weight loss



EPIDEMIOLOGY

INCIDENCE (US)

0.85 per 100,000 or 5,000 new cases per year.
this represent 3% of gastrointestinal cancers.

SEX RATIO

$M / F = 1.5$

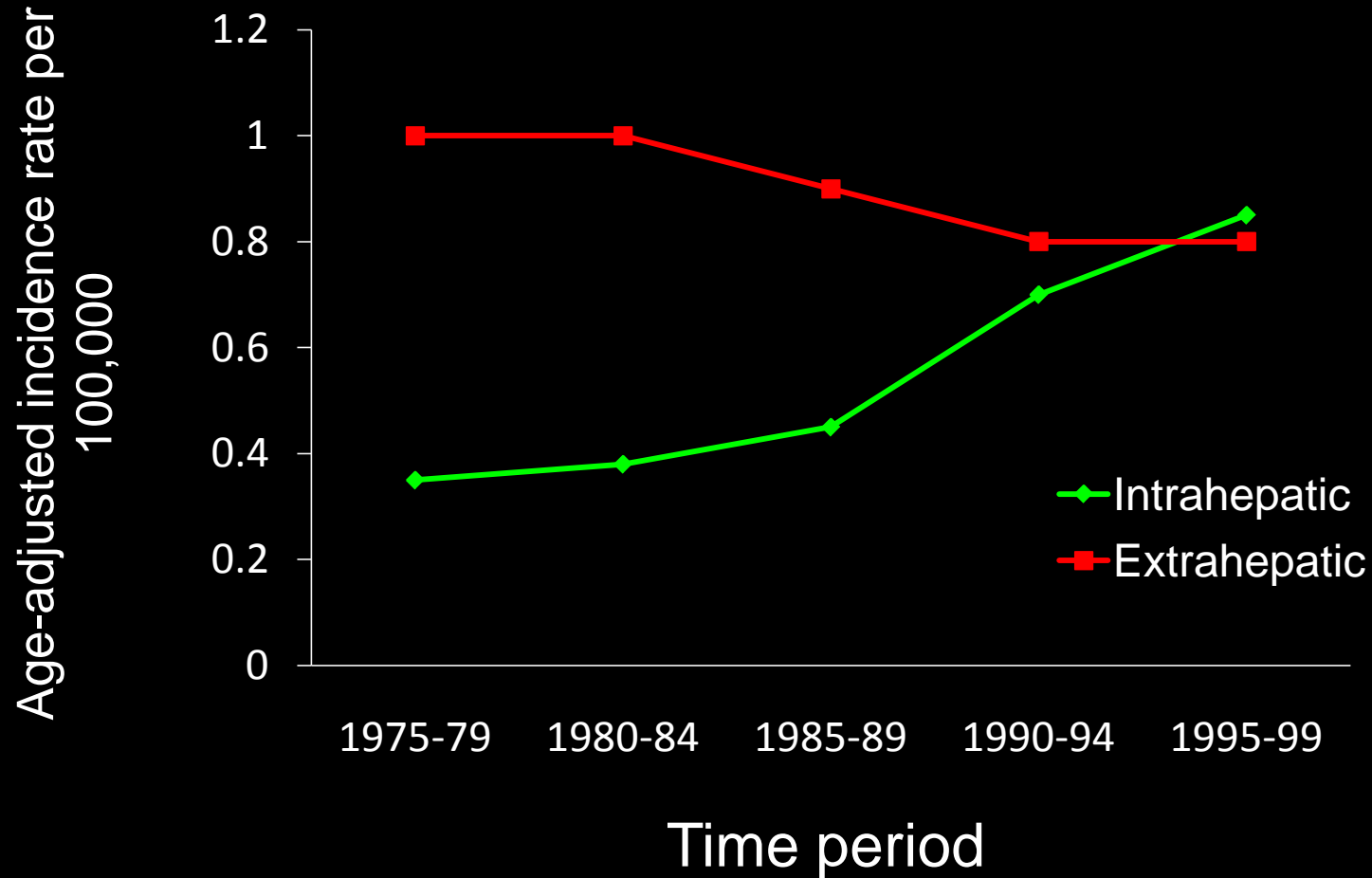
RACE DIFFERENCES

Asians are affected twice more commonly than Whites and Blacks.

EPIDEMIOLOGY

Age at diagnosis, years	44.2 ± 17.4	(11-81)
Males, <i>n</i> (%)	101 (59.8)	
Ethnicity, <i>n</i> (%)		
White	51 (30.2)	
African American	15 (8.9)	
Hispanic	9 (5.3)	
Asian/Pacific Islander	3 (1.8)	
Other/Unknown	91 (53.8)	
Laboratory Values at Diagnosis		
Alkaline Phosphatase, IU/L	283.4 ± 256.8	(30 – 1355)
Aspartate Aminotransferase, IU/L	66 ± 65.7	(13 – 407)
Alanine Aminotransferase, IU/L	70.3 ± 71.9	(11 – 339)
Total bilirubin, g/dL	2.3 ± 3.7	(0.2 - 19.7)
Serum albumin, g/dL	3.8 ± 0.8	(1.3 - 5.1)
International Normalized Ratio	1.1 ± 0.2	(0.9 - 2.7)
MELD	9.6 ± 4.1	(6.4 - 27.4)
IBD, <i>n</i> (%)	109 (64.5)	
Ulcerative colitis	95 (56.2%)	
Crohn's disease	13 (7.7%)	
Indeterminate colitis	1 (0.6%)	
Outcomes, <i>n</i>		
Liver Transplantation	23	
Cholangiocarcinoma	7	

US INCIDENCE TRENDS



CCA IN PRIMARY SCLEROSING CHOLANGITIS (PSC)

CCA WILL OCCUR IN APPROX 10% OF PSC CASES

cumulative lifetime incidence is 9-20%
lifetime risk is 0.5-1.5% /year.

median age of diagnosis:

- PSC patients → 30-50 years.
- other patients → > 65 years.

CCA SPARES SMALL DUCTS PSC

RISK FACTORS (I)

Definition: something that increases a person's chances of developing an event (disease).

ONLY 10% OF CCA ARE ASSOCIATED WITH
RECOGNIZED RISK FACTORS

Chronic biliary inflammation is the common underlying environment where CCA ensues

RISK FACTORS (II)

ESTABLISHED

- Liver fluke infestation (*Opisthorchis viverrini*)
- Choledochal cysts
- Hepatholitiasis
- Thorotrast infusion
- **PSC**

RISK FACTORS (III)

WEAKER

- Liver fluke infestation (*Clonorchis sinensis*)
- Alcohol intake
- Tobacco use
- Chronic viral hepatitis without cirrhosis
- BMI > 30 kg/m² (e.g. obesity)

OUTCOME / TREATMENT

An early diagnosis is crucial to allow surgery (and possibly liver transplant) as the preferred approach to change the prognosis for both IH and EH CCA

A strict PSC screening for CCA is debated in its frequency but strongly recommended

IH-CCA DIAGNOSIS

Usually easier, follows these steps

- detection of a liver lesion at US or CT scan
- US- or CT-guided biopsy / histology
- exclusion of EH primitive cancer localizations

EH-CCA DIAGNOSIS

CLINICALLY, malignancy is suspected in the presence of:

- Persistent jaundice
- Persistent pruritus
- Weight loss
- Abdominal pain
- Rapidly increasing serum bilirubin

Diagnose EH-CCA in PSC patients is notoriously challenging

> 50% CCA detected at the same time or within 1 year of diagnosis of PSC.

OFTEN MIMICKING PSC OR END-STAGE LIVER DISEASE

IMAGING TECHNIQUES (I)

- Ultrasonography (US)
- Computer tomography (CT)
- Magnetic resonance cholangio-pancreatography (MRCP)
- Endoscopic retrograde cholangio-pancreatography (ERCP)

IMAGING TECHNIQUES (I)

- Endoscopic ultrasonography (EUS)
- Intraluminal cholangioscopy (IC)
- Positron emission tomography (PET)

EUS-guided fine-needle biopsy has 100% PPV and 91% sensitivity in suspected CCA.

SERUM MARKERS

Markers sensitivity and specificity change in various pathological conditions

Clinical significance is not univocal and remains controversial

- CARBOHYDRATE ANTIGEN 19-9 (CA 19-9)

≤ 40 u/ml

NPV 94%

> 129 u/ml

PPV 100% (liver cysts)

- CARCINOEMBRYONIC ANTIGEN (CEA)

> 5 µg/l

specif 86%

sensit 55%

(debated results)

BRUSH CYTOLOGY

Biliary cells sample obtained at ERCP through the brushing of observed strictures

Sensitivity: below 50% but it improves w/ sampling

Specificity: 97-100%.



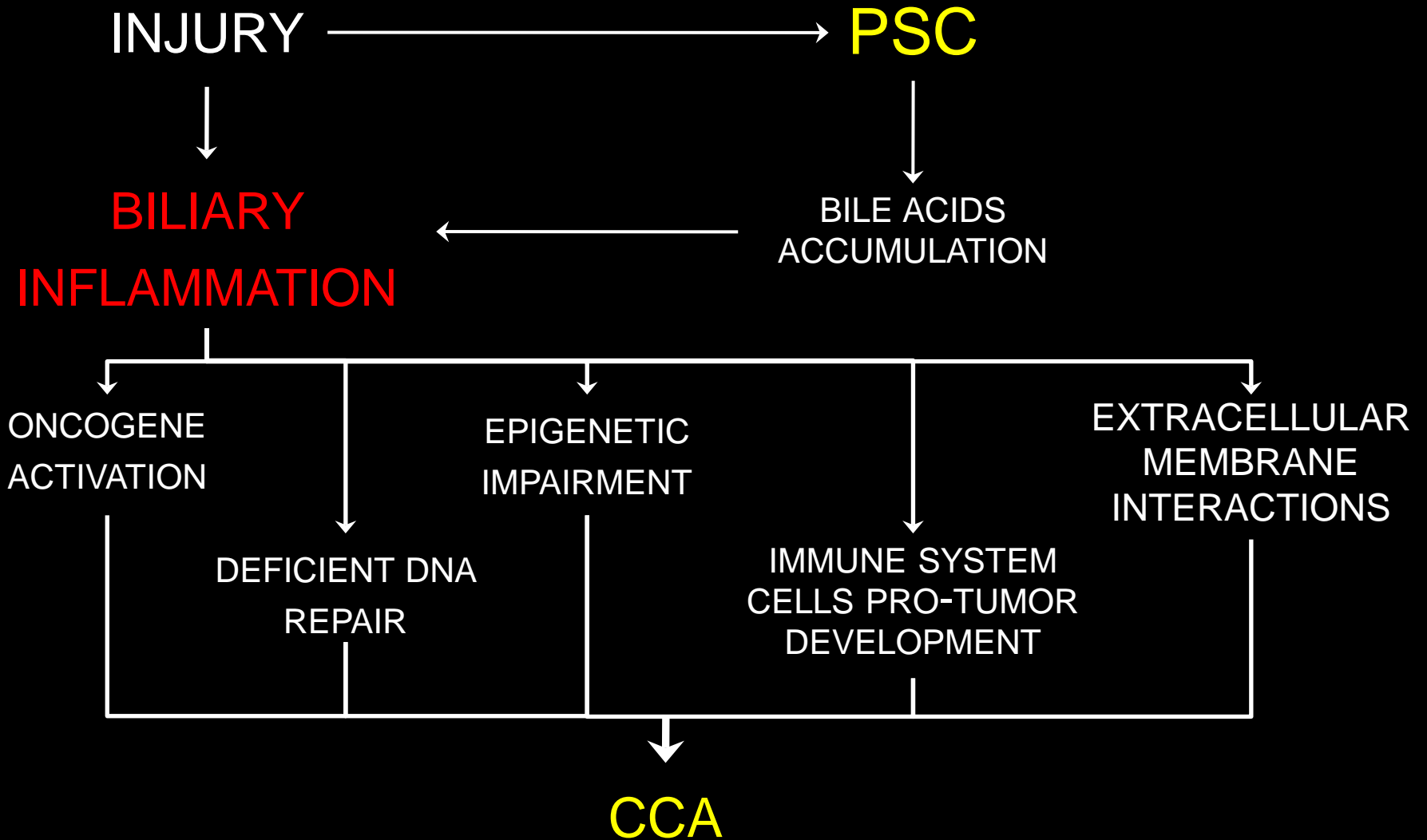
PATHOGENESIS (I)

Most likely, the development of CCA is the result of the breakdown of a fine balance between multiple elements

PATHOGENESIS (II)

- GENETIC PREDISPOSITION → MUTATIONS / SNP
- ENVIRONMENTAL STIMULI → INFLAMMATION
BILIARY INJURY
- EPIGENETIC REGULATION → DNA METHYLATION
MICRO-RNA

PATHOGENESIS (III)



PATHOGENESIS (IV)

CCA can ensue at any level of biliary tree and this observation may be explained by the “FIELD EFFECT” (similar to breast and lung cancer)

The exposure of a homogeneous cell population (biliary epithelium in PSC) to the action of same carcinogenic factors

EVERY CELL COULD BE CONVERTED INTO A CANCER CELL

THE RESOLUTION OF A NEOPLASTIC EVENT DOES NOT EXCLUDE OTHERS

MOLECULAR PATHWAYS (I)

ENHANCED/OVEREXPRESSED

FUNCTIONAL CONSEQUENCE

TNF α

Pro-inflammatory status

IL-6

Pro-inflammatory status

Cyclin D1

Stimulate cells cycle

MAPK13p/p38 δ /SAPK4

Increases motility of CCA cells

MiRNA-21

Suppression of PDCD4, TIMP3 and PTEN (stimulation tumor suppression by apoptosis)

MOLECULAR PATHWAYS (II)

DECREASE

FUNCTIONAL CONSEQUENCE

B-catenin, E-cadherin

Decrease intracellular adhesion

mir-204, mir-320

Suppress antiapoptotic Bcl-2

MUTATED

FUNCTIONAL CONSEQUENCE

p53 (30-80%)

Deregulation of cell cycle arrest or apoptosis

K-ras

Mutated gene can permanently activate cell proliferation

CONCLUSIONS

- High prevalence at autopsy (30 - 40%) and OLT (23 - 33%)
- Cumulative incidence ranging from 4% to 20% in 5 to 12 years follow-up
- Suspicion raised at cholangiography by marked or progressive ductal dilatation, progressive stricture, polypoid mass lesion $> 1 \text{ cm } \varnothing$
- Diagnosis for IH CCA in PSC is challenging (cytology has low sensitivity)

INTESTINAL FLORA

Thousands of commensal bacterial and fungal species generate a complex micro-environment called:

“INTESTINAL FLORA”.

It grows and co-evolves with the host, participating to:

- *DIGESTION OF NUTRIENTS*
- *PROTECTION OF MUCOSA*
- *DEVELOPMENT OF A HEALTHY GUT*
- *THE EVOLUTION OF A BALANCED MUCOSAL IMMUNE SYSTEM.*



PROBIOTICS

Intestinal flora status can be influenced by administration of exogenous PROBIOTICS.

WHO: "PROBIOTICS ARE LIVE MICROORGANISMS WHICH, WHEN CONSUMED IN ADEQUATE AMOUNTS AS PART OF FOOD, CONFER A HEALTH BENEFIT ON THE HOST".

MECHANISMS OF ACTION

Several studies demonstrate the great properties of immunomodulation on intestinal epithelial cells (IEC) and immune system cells (ISC).

Probiotics explain their actions through:

- *PRODUCTION OF ANTIBACTERIAL SUBSTANCES*
- *SECRETION OF MUCOSAL CYTOPROTECTIVE AGENTS*
- *COMPETITIVE INHIBITION OF PATHOGENS ADHERENCE*
- *ENHANCING BARRIER FUNCTION AND IMMUNE ROLES OF IEC*
- ***REGULATION OF MUCOSAL IMMUNE RESPONSES***

IMMUNOMODULATORY ACTIVITY

Probiotics regulate immunologic responses balancing the interactions between exogenous microorganisms and local ISC in both hyper or hypo activation status.

- *ENHANCING HOST INNATE IMMUNITY*
- *INCREASING ANTI-INFLAMMATORY CYTOKINES*
- *SUPPRESSING PRO-INFLAMMATORY CYTOKINES*
- *UP-REGULATING HOST DEFENCES AGAINST INFECTION*

PROBIOTICS AND INFLAMMATORY BOWEL DISEASES (IBD)

THE INTAKE OF PROBIOTICS COULD IMPROVE PATIENTS CONDITIONS REDUCING BOWEL DISEASE ACTIVITY.

RATIONALE:

Hypothesis of an abnormal immune response against commensal flora.

STUDIES EVIDENCES:

Double blind clinical trials conducted with probiotic mixture (VSL#3). It is able to prevent chronic relapsing pouchitis.

PROBIOTICS AND PSC

RATIONALE:

- 90% of PSC patients are affected by IBD.
- The main hypothesis refers PSC as a translocation of a pathologic process from the bowel to the liver.

AIM:

- Liver damage could be **REDUCED** extinguishing IBD activity.
- Monitoring bowel disease it will be able to **PROTECT** and **PREVENT** biliary tree damage.

RESULTS:

Nowadays there is not any clinical trials that sustains the use of probiotics in PSC patients. **Further studies are required.**

VANCOMYCIN (I)

Bactericidal antibiotic poorly adsorbed by intestinal tract.

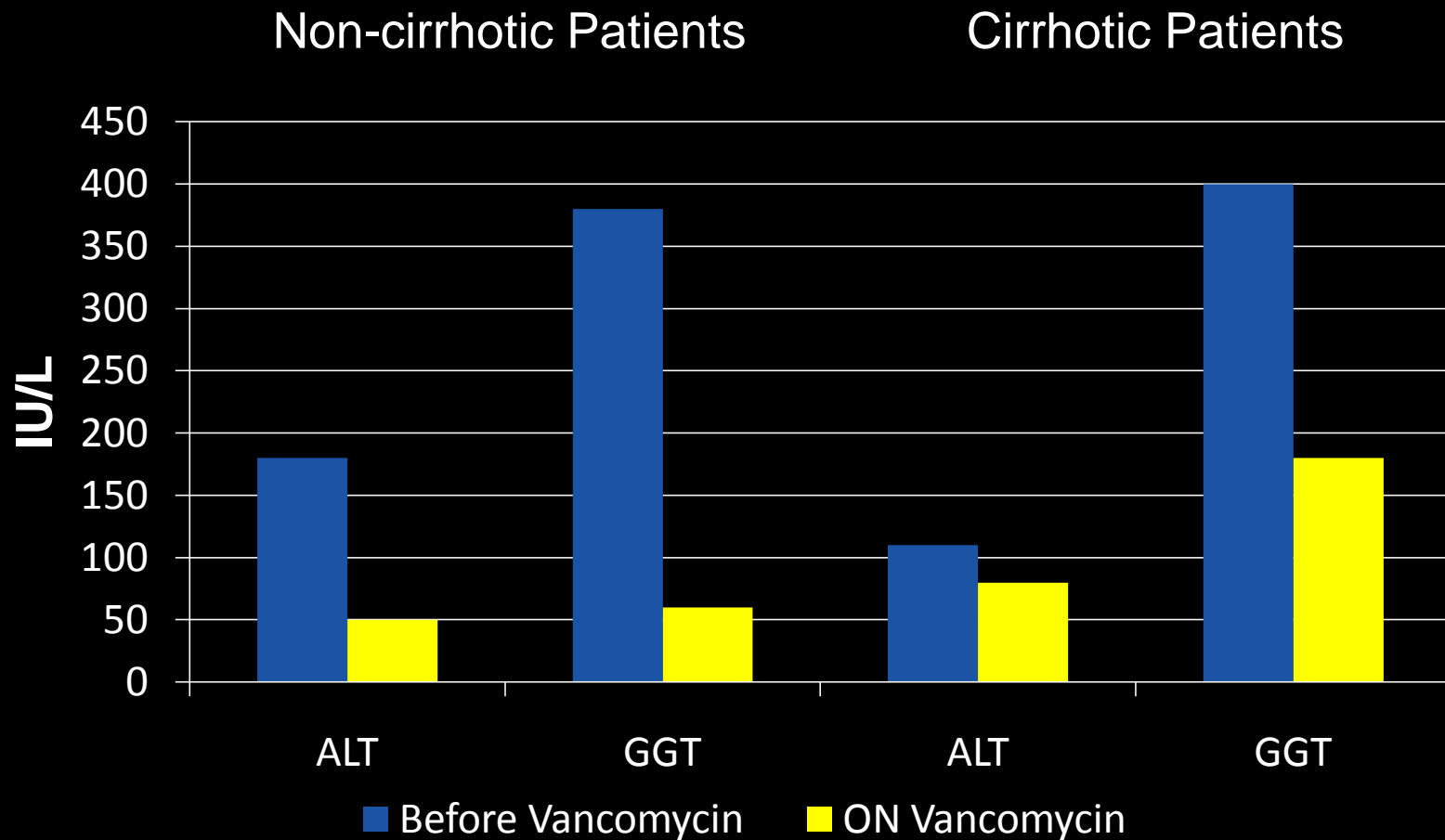
ACTION:

Given orally it acts killing gut Gram positive bacteria, modifying the composition of intestinal flora.

CLINICAL EVIDENCE:

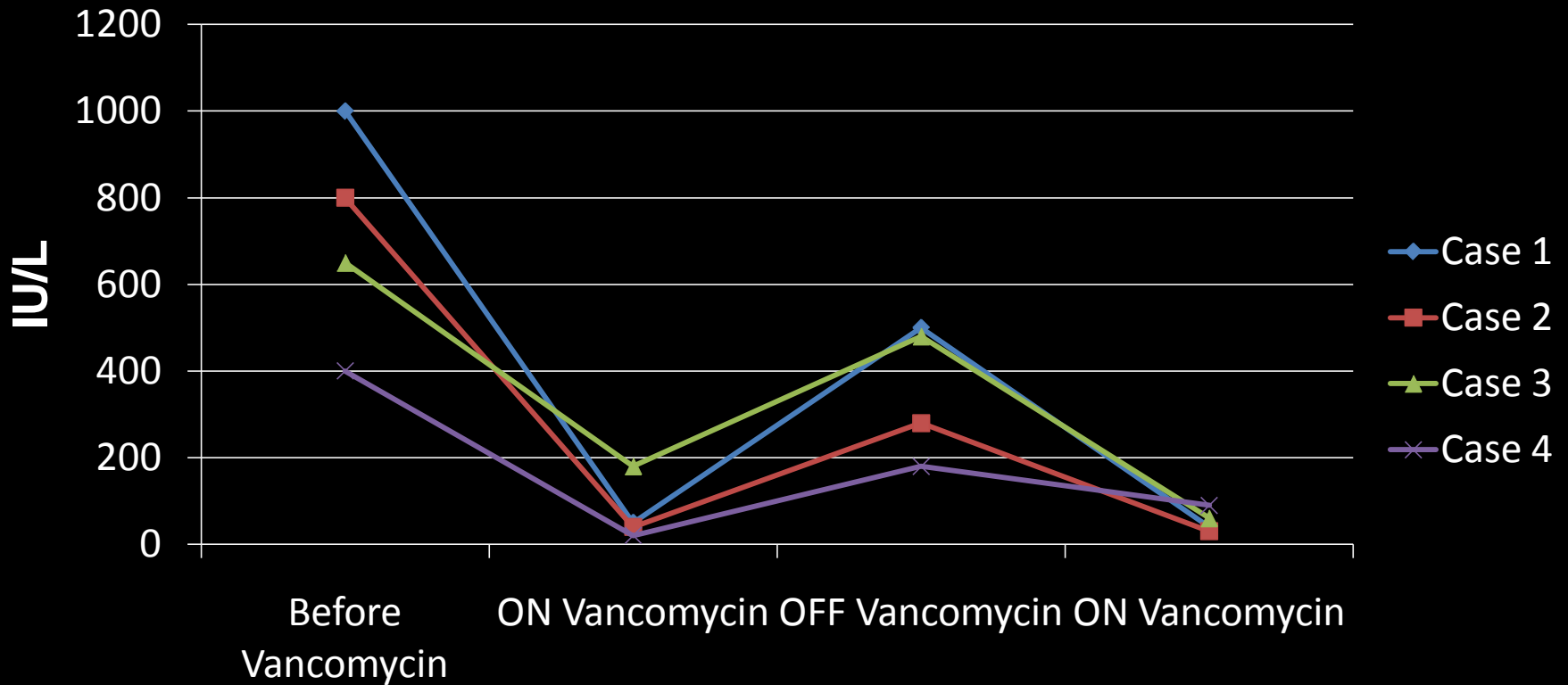
A study on 14 PSC + IBD pediatric patients treated only with sulfasalazine and vancomycin (50mg/kg die) shows the **EFFICACY** of the antibiotic therapy.

VANCOMYCIN (II)



VANCOMYCIN (III)

GGT cirrhotic patients



VANCOMYCIN (IV)

ALT cirrhotic patients

