Surgical Approach to Primary Sclerosing Cholangitis and Cholangiocarcinoma

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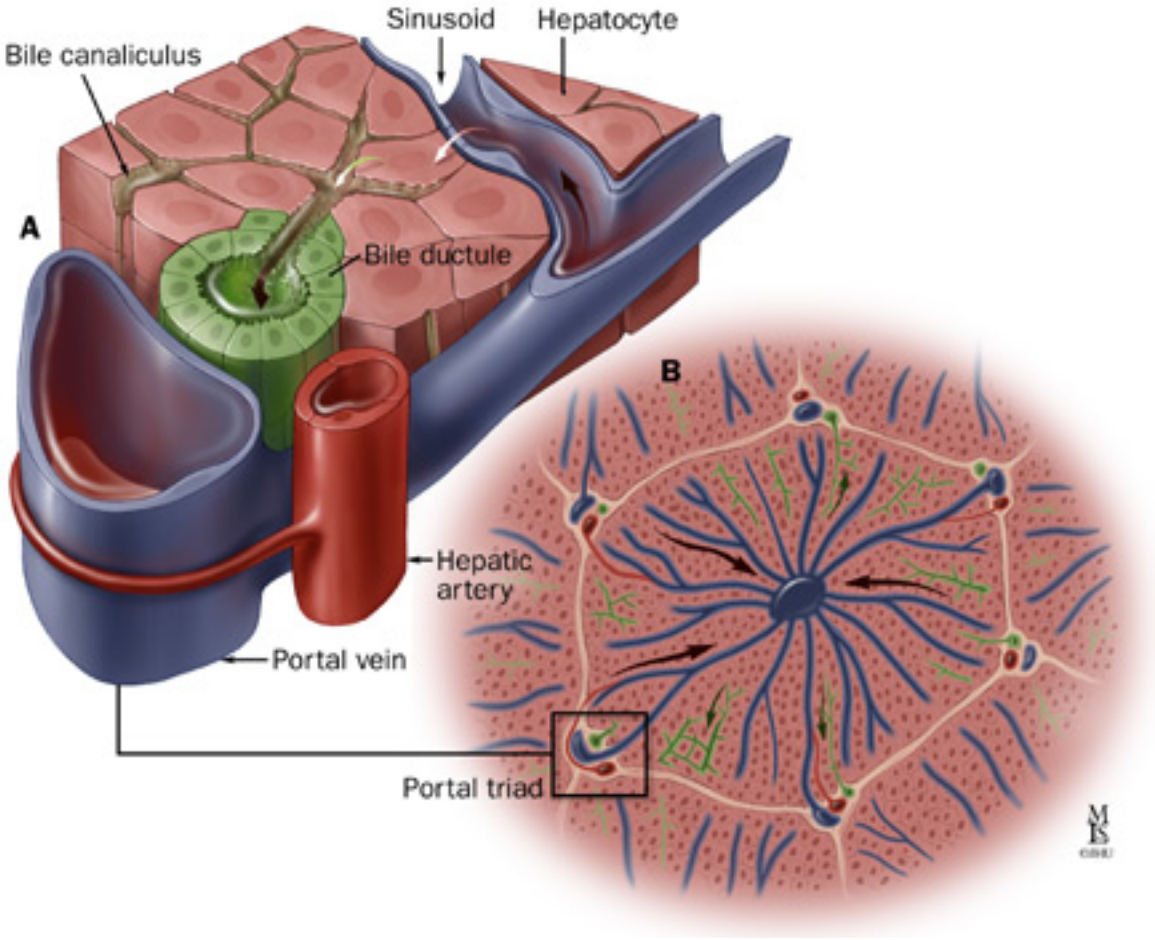
Objectives

- introduction to PSC
- surgical evaluation of those with PSC
- relationship of CCA with PSC
- description of imaging
- surgical resection options
- results of surgical intervention
- future directions

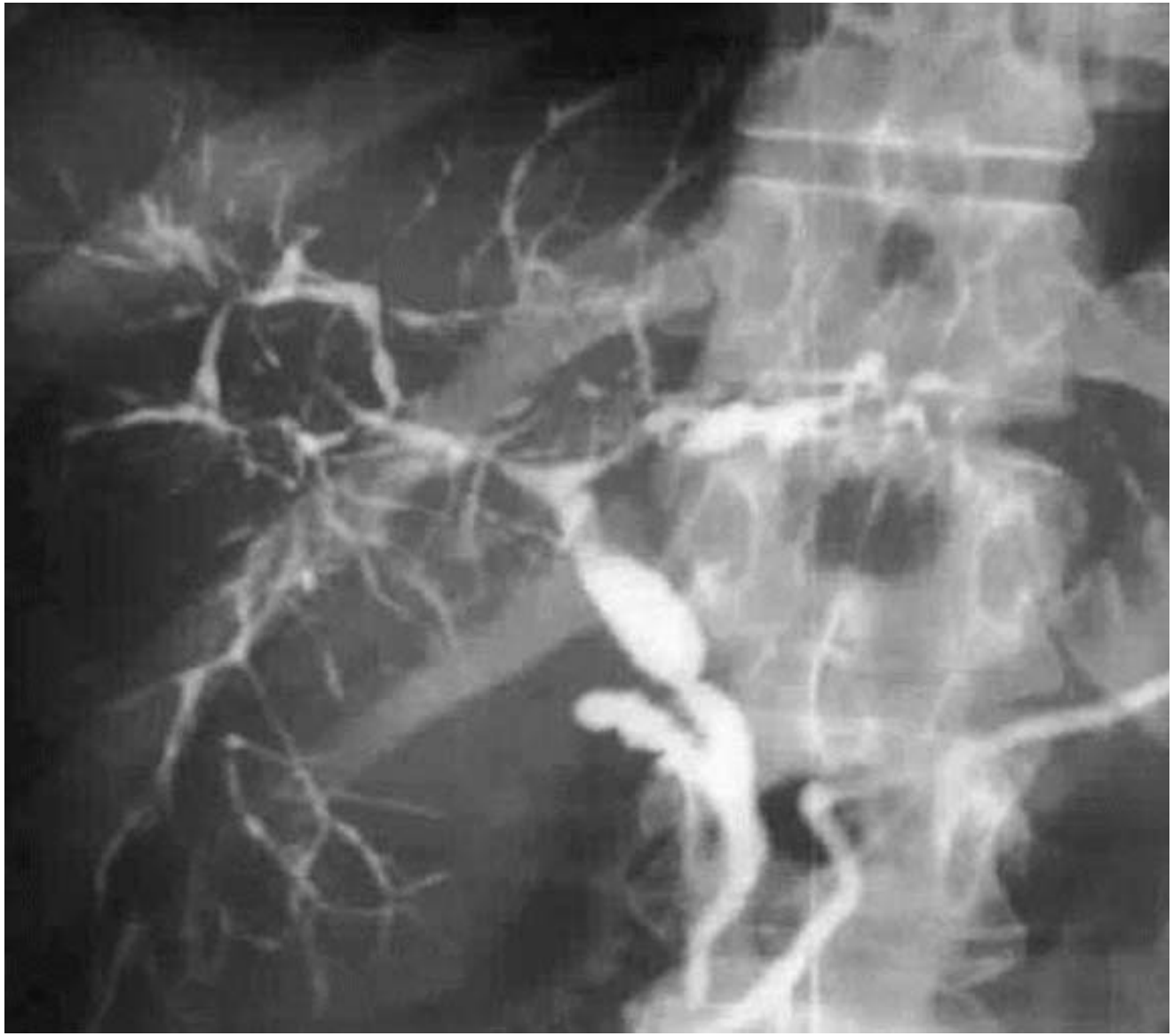
Introduction

- PSC is a disease with an uncertain etiology and progressive course
- chronic inflammation of the bile ducts results in scarring and liver damage
- non-transplant surgical procedures have a limited but well-defined role
- bile duct cancer is a significant risk in setting of PSC


Sinusoid
Hepatocyte
Bile canaliculus
A
Bile ductule
B
Hepatic artery
Portal vein
Portal triad

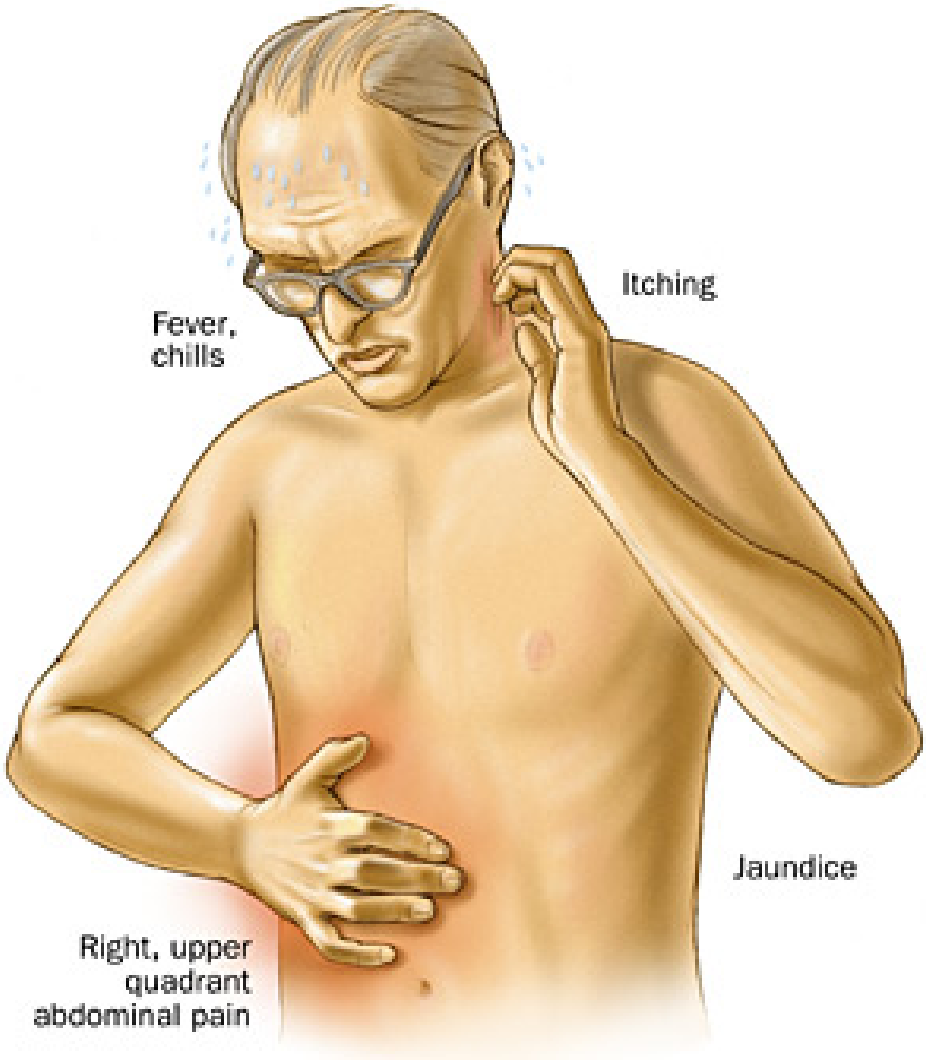
Epidemiology of PSC

- occurs at rate of 1 - 6/100,000
- more prevalent in men (60 - 70%)
- mean age of diagnosis: 36 y
- associated with UC
    - higher incidence of colorectal ca in those with both PSC and UC
    - 65-75% with PSC have IBD (UC or Crohn's)
    - 3-10% of those with UC have PSC



Natural History

- many patients remain asymptomatic for years, yet others will rapidly develop advanced disease
- symptoms of fatigue, itching and jaundice within several years of diagnosis
- progression to portal hypertension and cirrhosis ensues, and once liver failure develops, liver transplantation is the only therapeutic option
- increased risk for developing cholangiocarcinoma… with a lifetime incidence of 10–30%


Fever,
chills
Itching
Jaundice
Right, upper
quadrant
abdominal pain

Treatment of PSC

- Ursodeoxycholic acid (Ursodiol®) has been the most extensively studied drug and has been shown to **improve serum liver function tests** and the **histological stage of disease on liver biopsy**
- methotrexate, tacrolimus, cladibrine, budesonide and colchicine have all been studied
- no clear-cut evidence that ***any*** treatment modality can slow the progression of PSC to cirrhosis

Surgical Evaluation

- surgeons are asked to evaluate patients with PSC where
  - a dominant stricture is present
  - cholangiocarcinoma is present
  - end-stage liver disease is present
  - gallbladder symptoms with stones
  - colon requires resection (UC)

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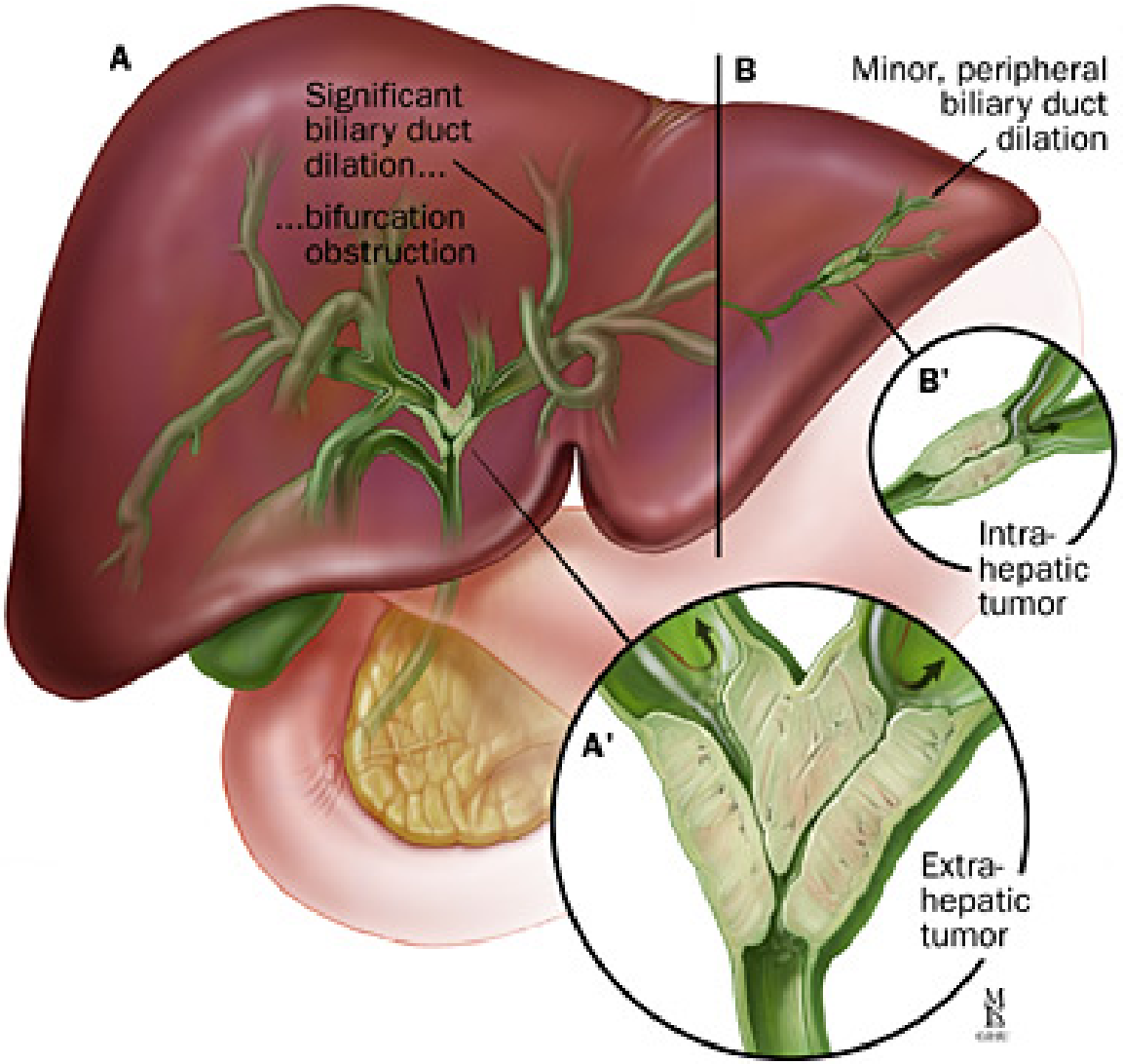
Surgery and PSC

- surgical procedures will not alter the course of PSC
- percutaneous and endoscopic interventions have supplanted much
- surgery reserved for complications:
  - suspicious strictures
  - cholecystitis
- cirrhotics are best served with Liver Transplantation

Cholangiocarcinoma

- cholangiocarcinoma (CCA) is an uncommon yet lethal disease
- 10 - 30% of those with PSC will develop CCA
- there are known risk factors (PSC) but the majority arise in those without them
- surgical resection remains the gold standard therapy (multi-modality with transplant)
- vast majority of patients will NOT be surgical candidates


A
B
Minor, peripheral biliary duct dilation
Significant biliary duct dilation...
...bifurcation obstruction
B'
Intra-hepatic tumor
A'
Extra-hepatic tumor

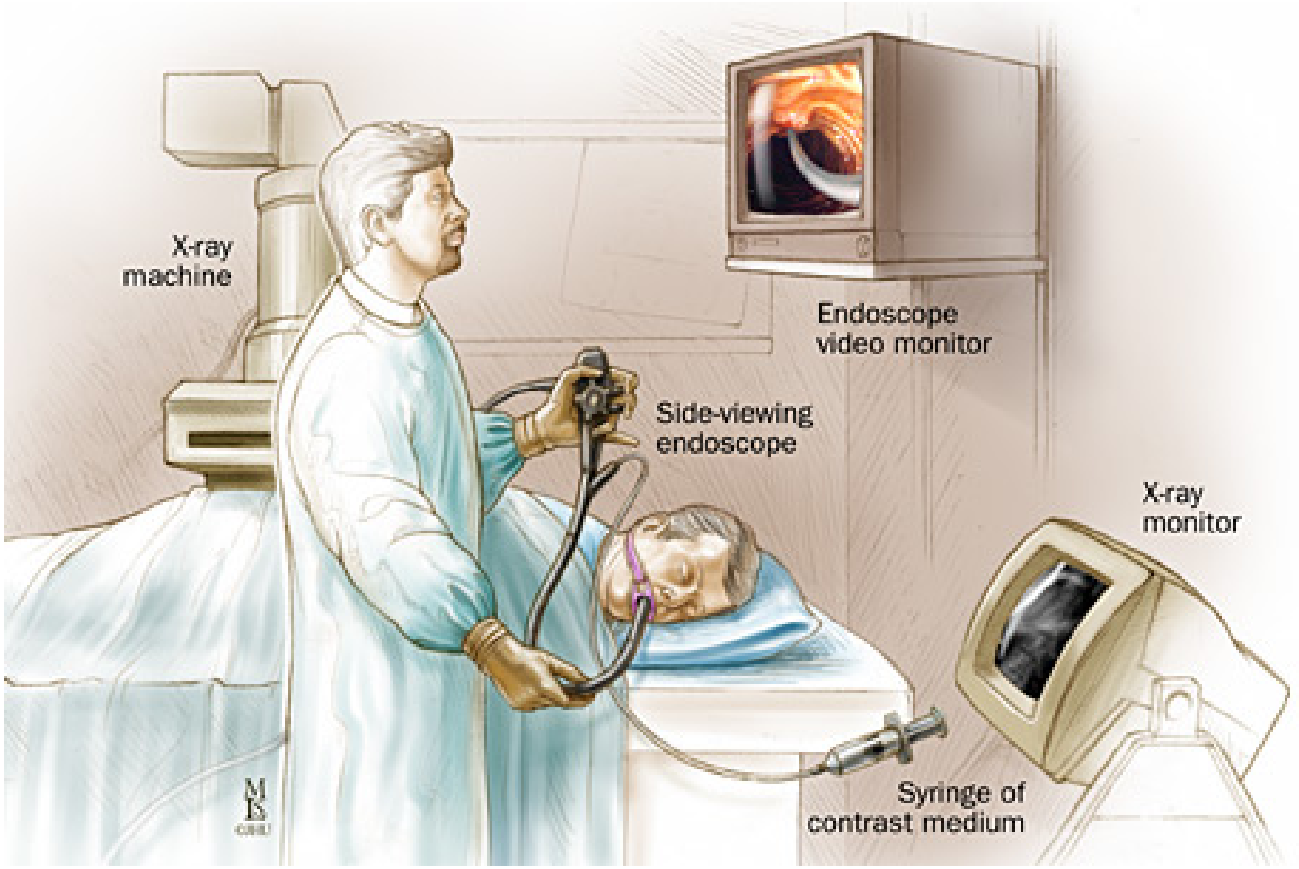

Coca-Cola

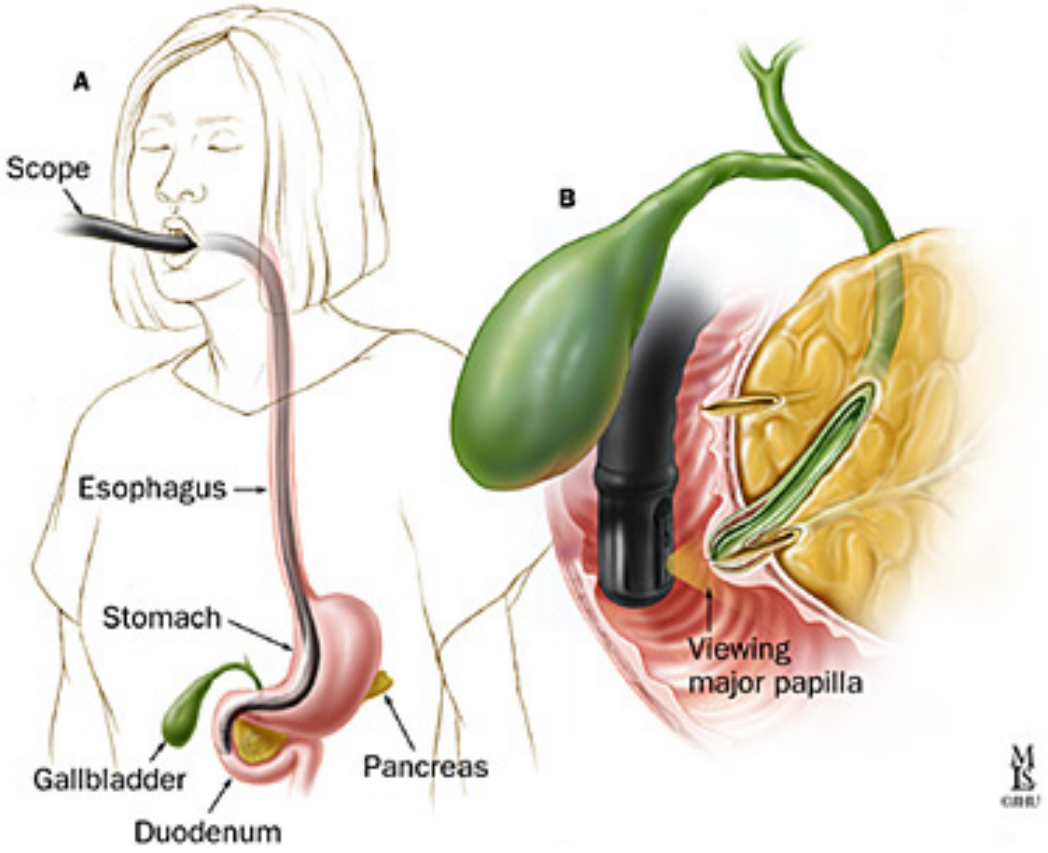
Clinical Presentation of CCA

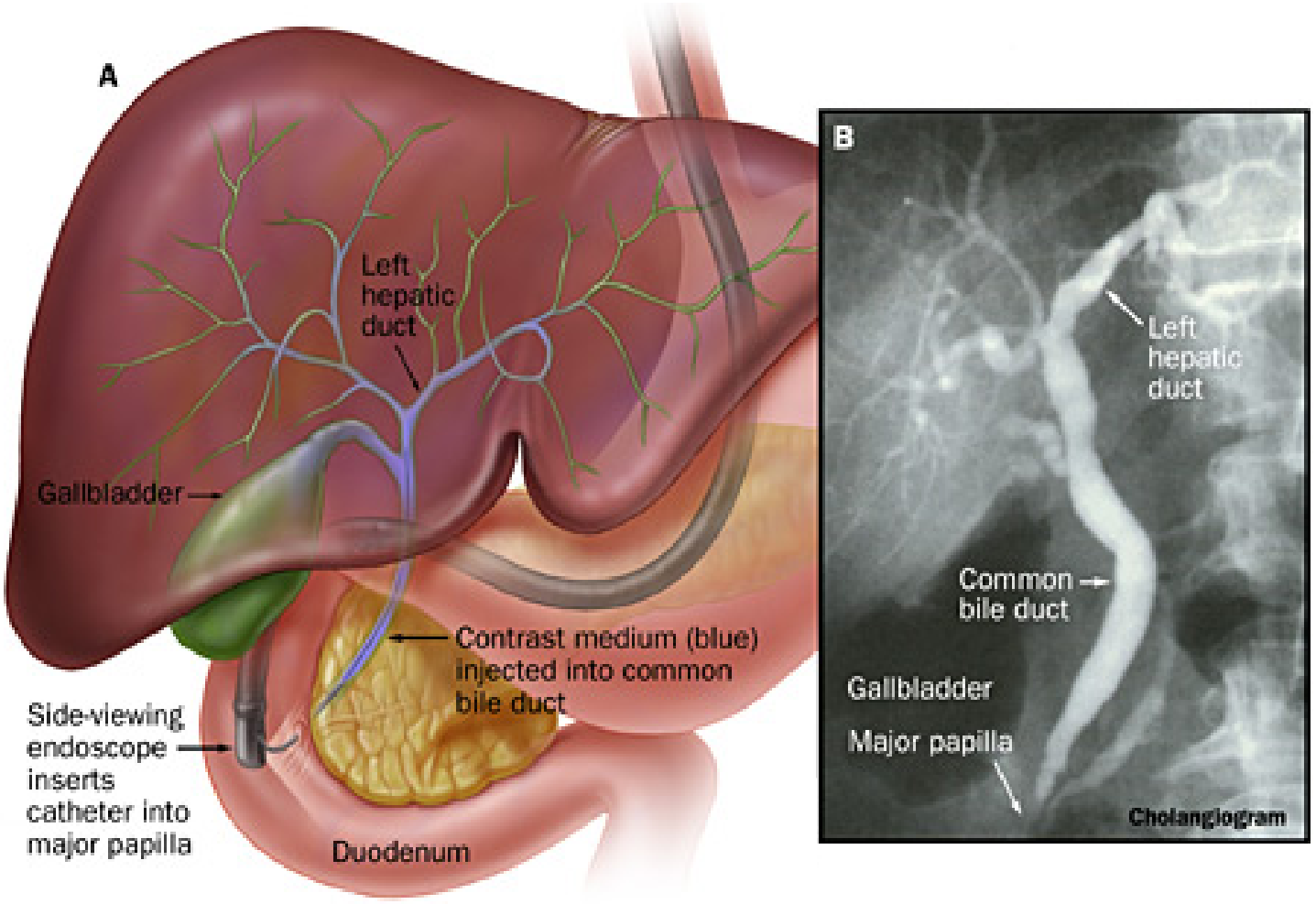
- jaundice, weight loss, abdominal pain
- elevated liver enzymes
- risk factors
  - age
  - gallstones
  - PSC
  - liver flukes (*Clonorchis sinensis*, etc.)
  - cirrhosis
  - congenital biliary cysts
  - others (smoking, Thorotrast®, etc.)

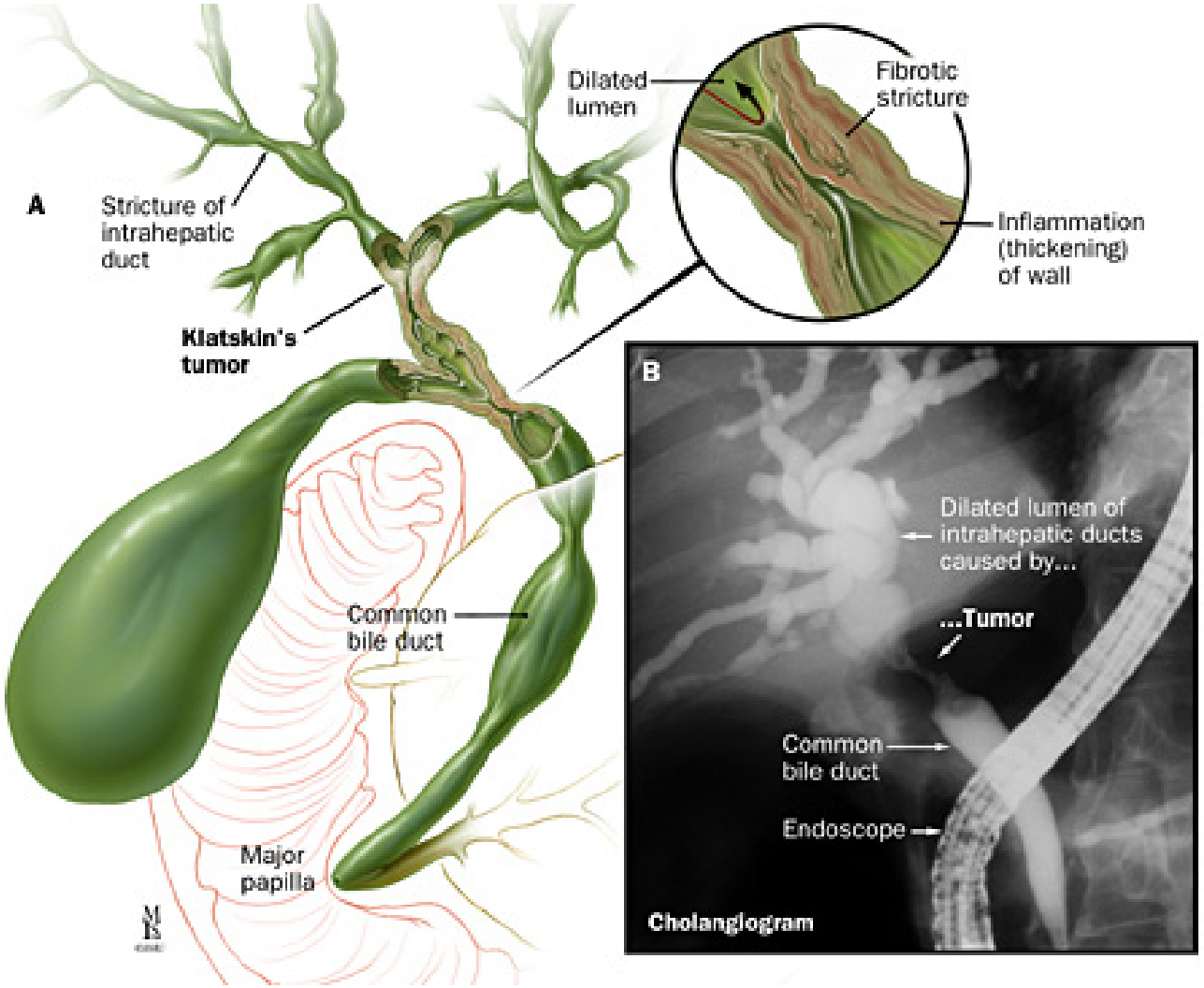
Surgical Evaluation

- History and Physical Examination
- blood work (including tumor markers)
- evaluate status of heart, lungs, kidneys
- radiologic exams
  - US, CT, MR, percutaneous
- endoscopic procedures
  - upper, lower, ERCP
- cytology (cellular analysis)


X-ray machine
Endoscope video monitor
Side-viewing endoscope
X-ray monitor
Syringe of contrast medium


A
Scope
Esophagus
Stomach
Gallbladder
Duodenum
Pancreas
B
Viewing
major papilla


A
Left hepatic duct
Gallbladder
Contrast medium (blue) injected into common bile duct
Side-viewing endoscope inserts catheter into major papilla
Duodenum
B
Left hepatic duct
Common bile duct
Gallbladder
Major papilla
Cholangiogram


A
Stricture of intrahepatic duct
Klatskin's tumor
Common bile duct
Major papilla
Dilated lumen
Fibrotic stricture
Inflammation (thickening) of wall
B
Dilated lumen of intrahepatic ducts caused by...
...Tumor
Common bile duct
Endoscope
Cholanglogram

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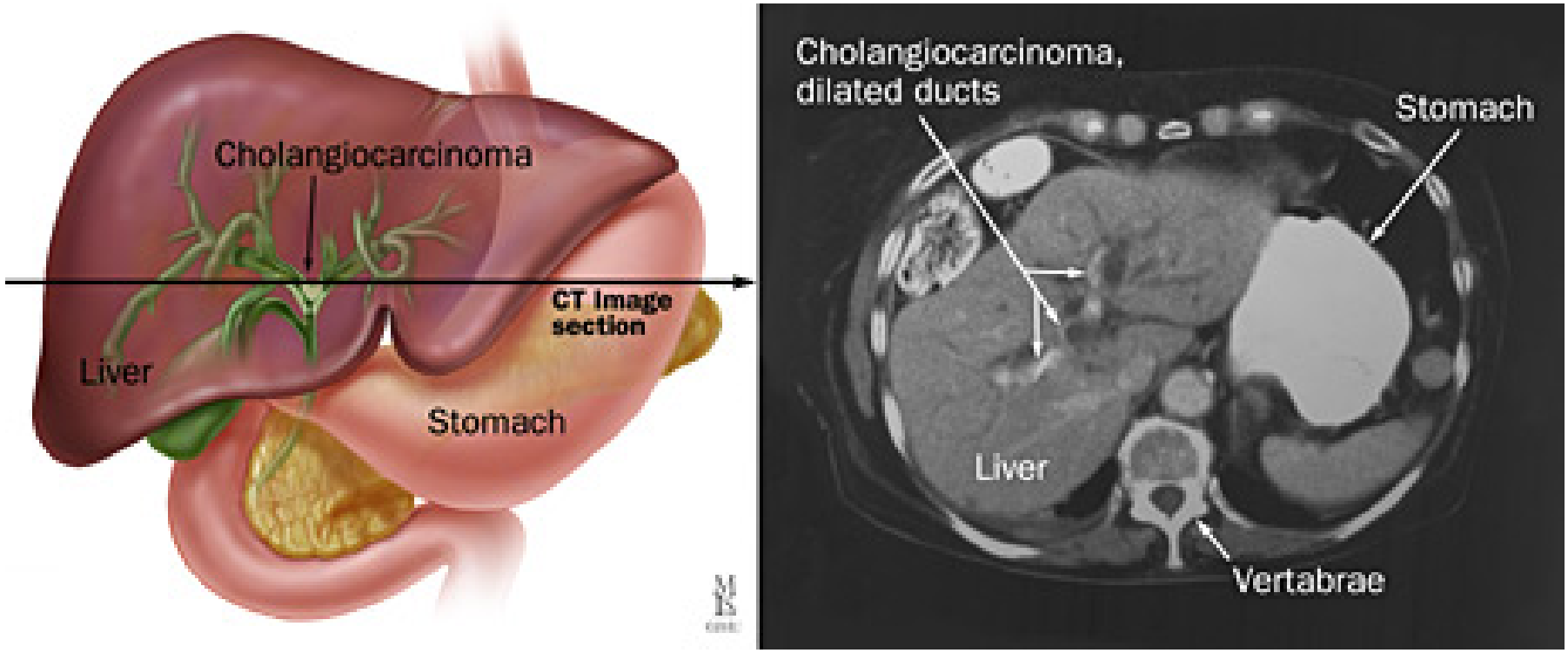
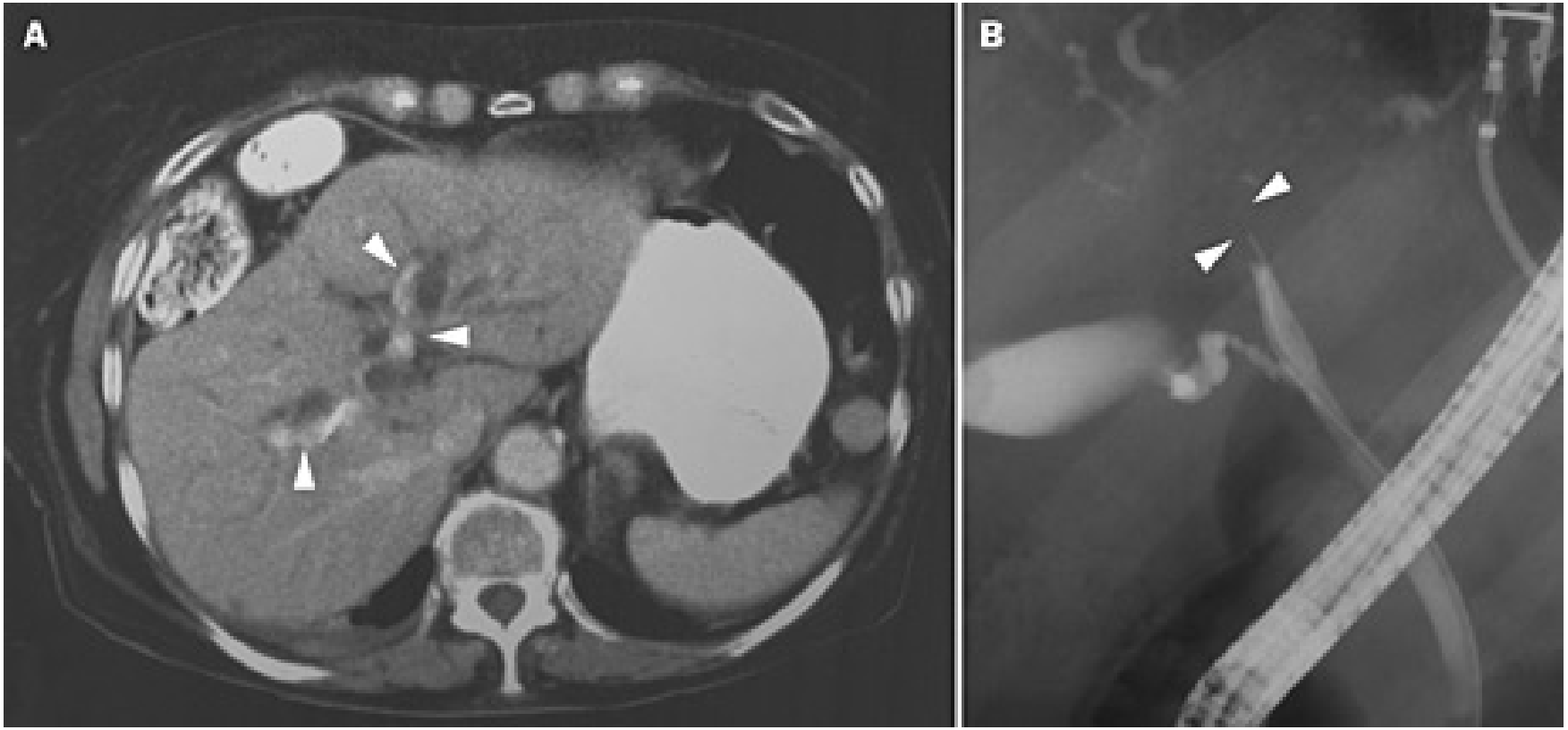

Cholangiocarcinoma
CT Image section
Liver
Stomach
Cholangiocarcinoma, dilated ducts
Stomach
Liver
Vertabrae



PET scan for CCA

36 year-old male patient with probable cholangiocarcinoma.

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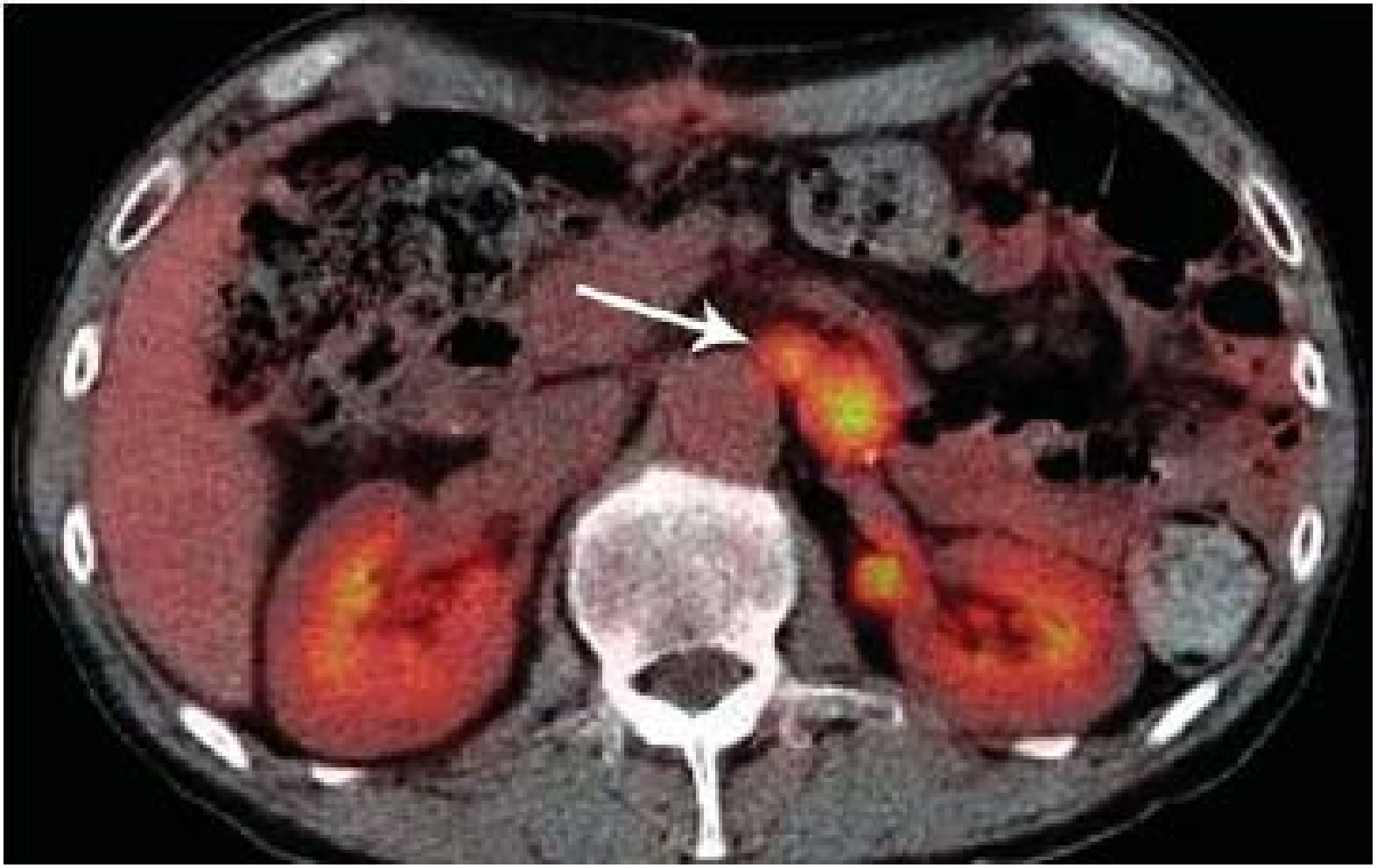
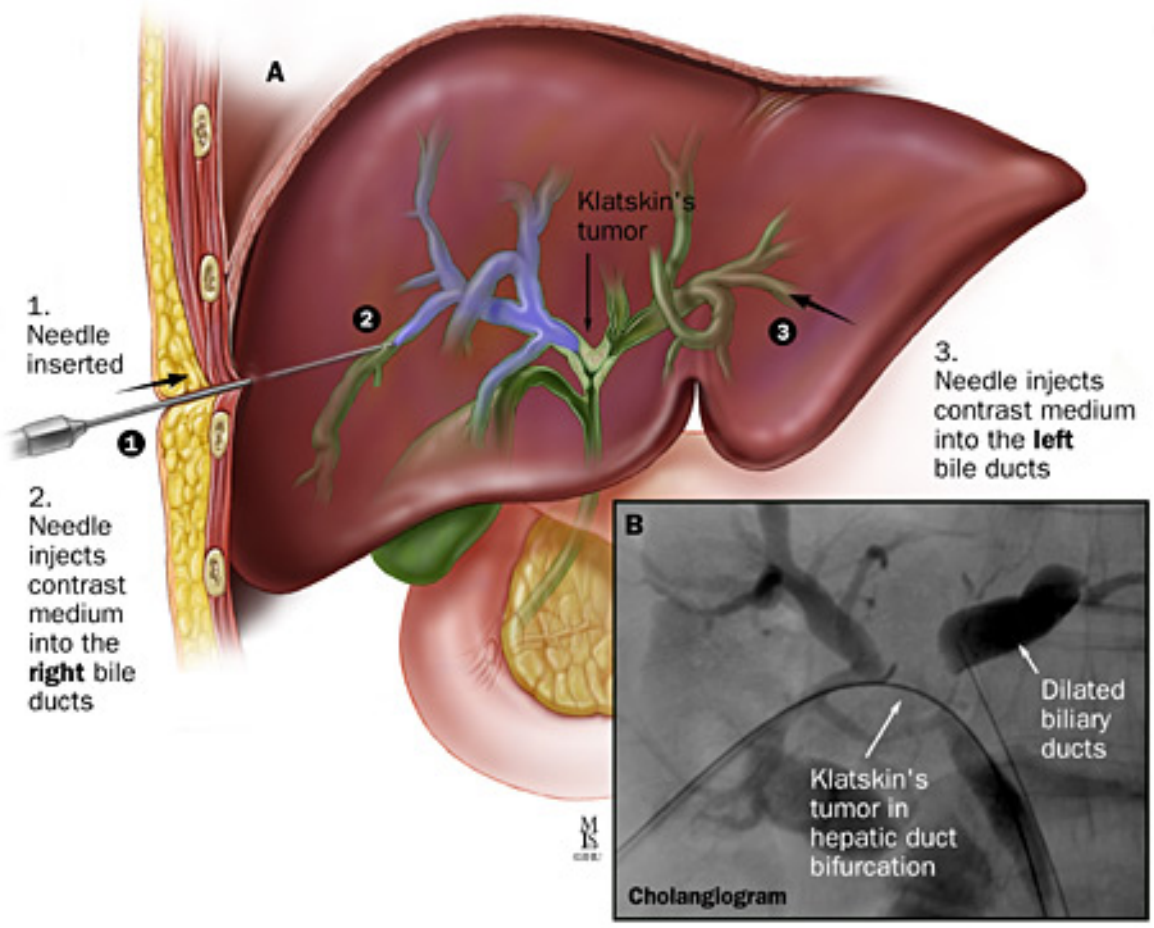
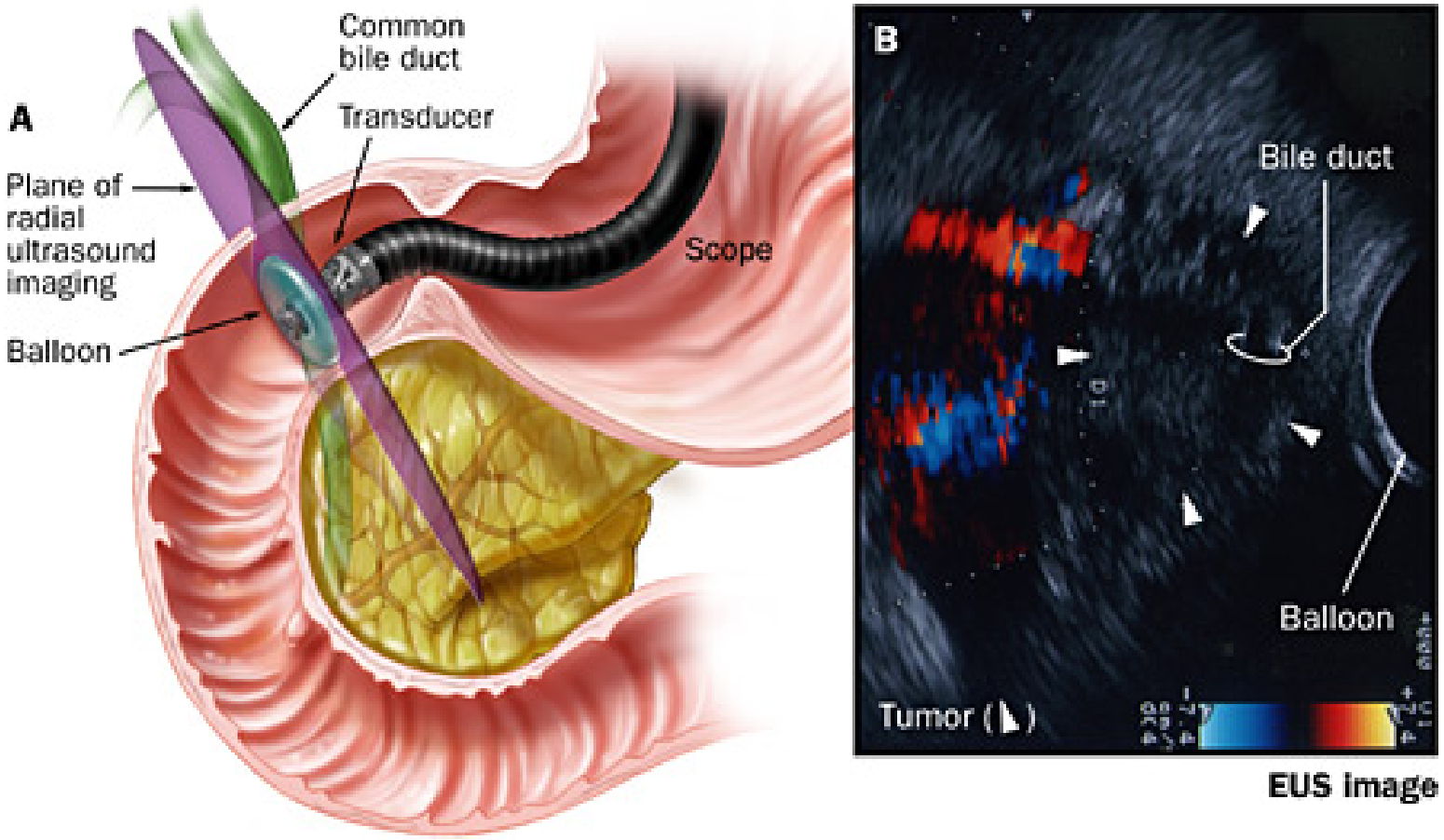



A
Klatskin's tumor
1. Needle inserted
2. Needle injects contrast medium into the **right** bile ducts
3. Needle injects contrast medium into the **left** bile ducts
B
Dilated biliary ducts
Klatskin's tumor in hepatic duct bifurcation
Cholanglogram



EUS image

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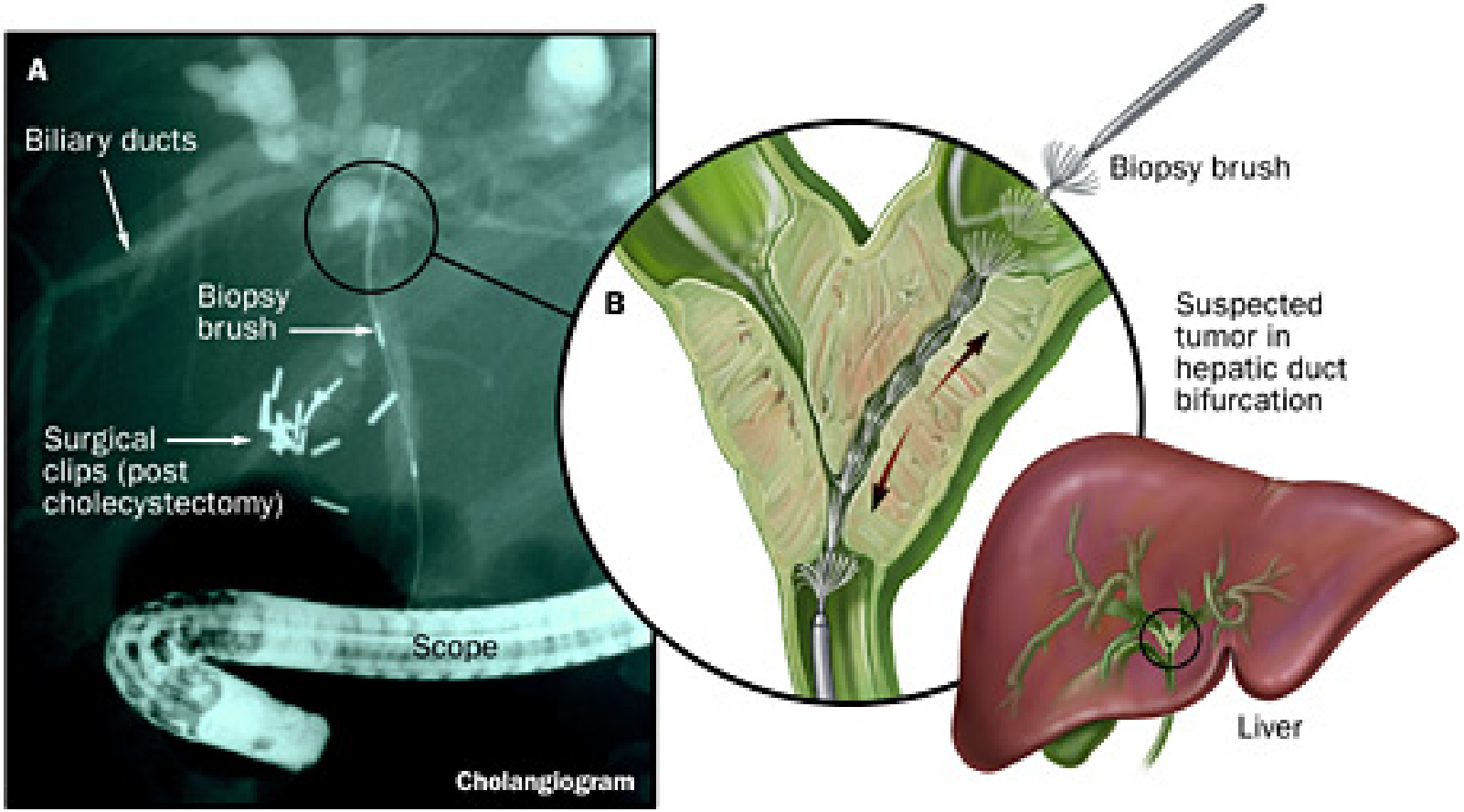
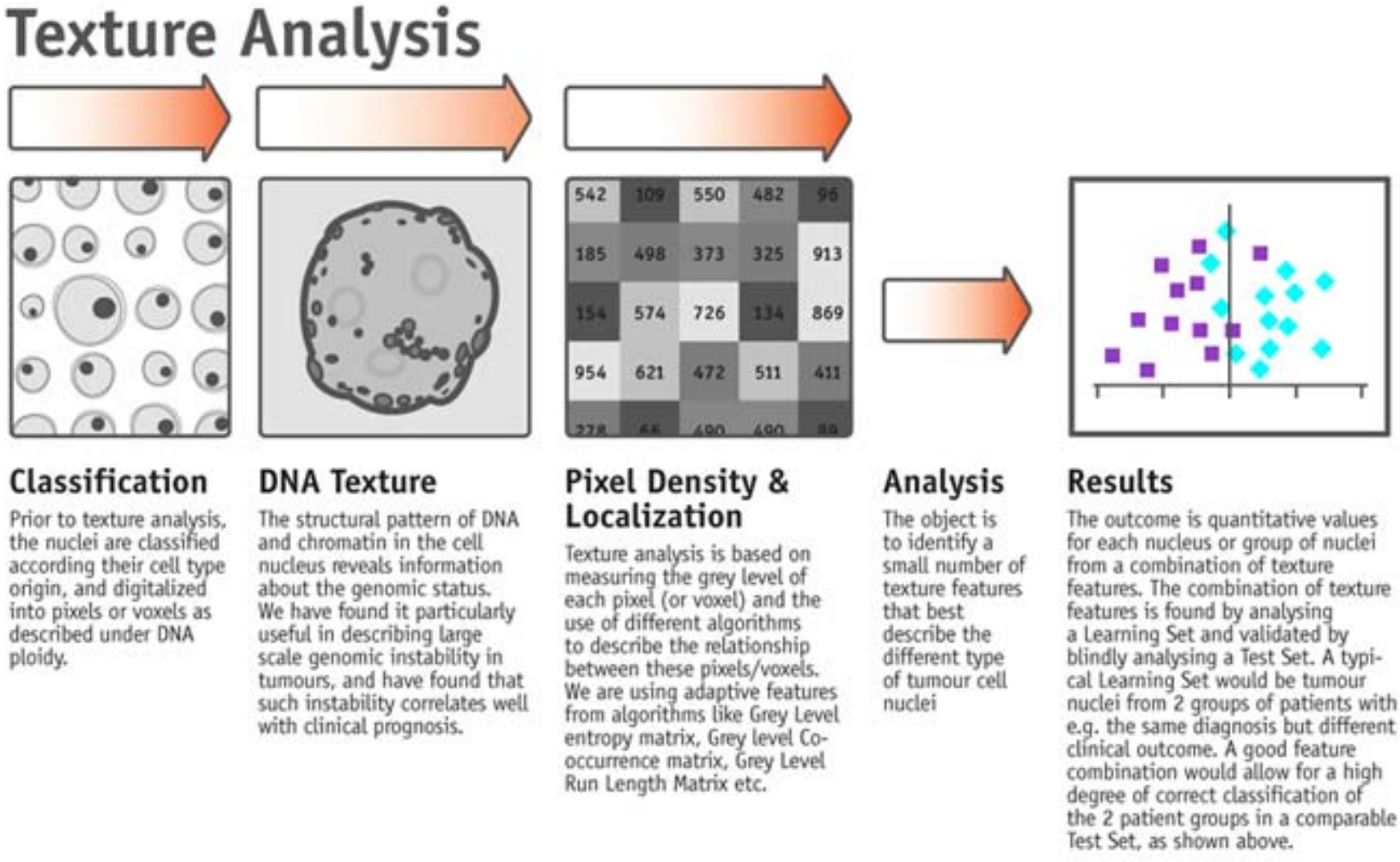
Diagnosis

- ***cytology*** via endoscopic or percutaneous techniques
- ***digitized image analysis*** (DIA) and ***fluorescence in situ hybridization*** (FISH) offer promise to evaluate extrahepatic bile duct lesions for cellular aneuploidy and chromosomal aberrations


A
Biliary ducts
Biopsy brush
Surgical clips (post cholecystectomy)
Scope
Cholangiogram
B
Biopsy brush
Suspected tumor in hepatic duct bifurcation
Liver

DIA



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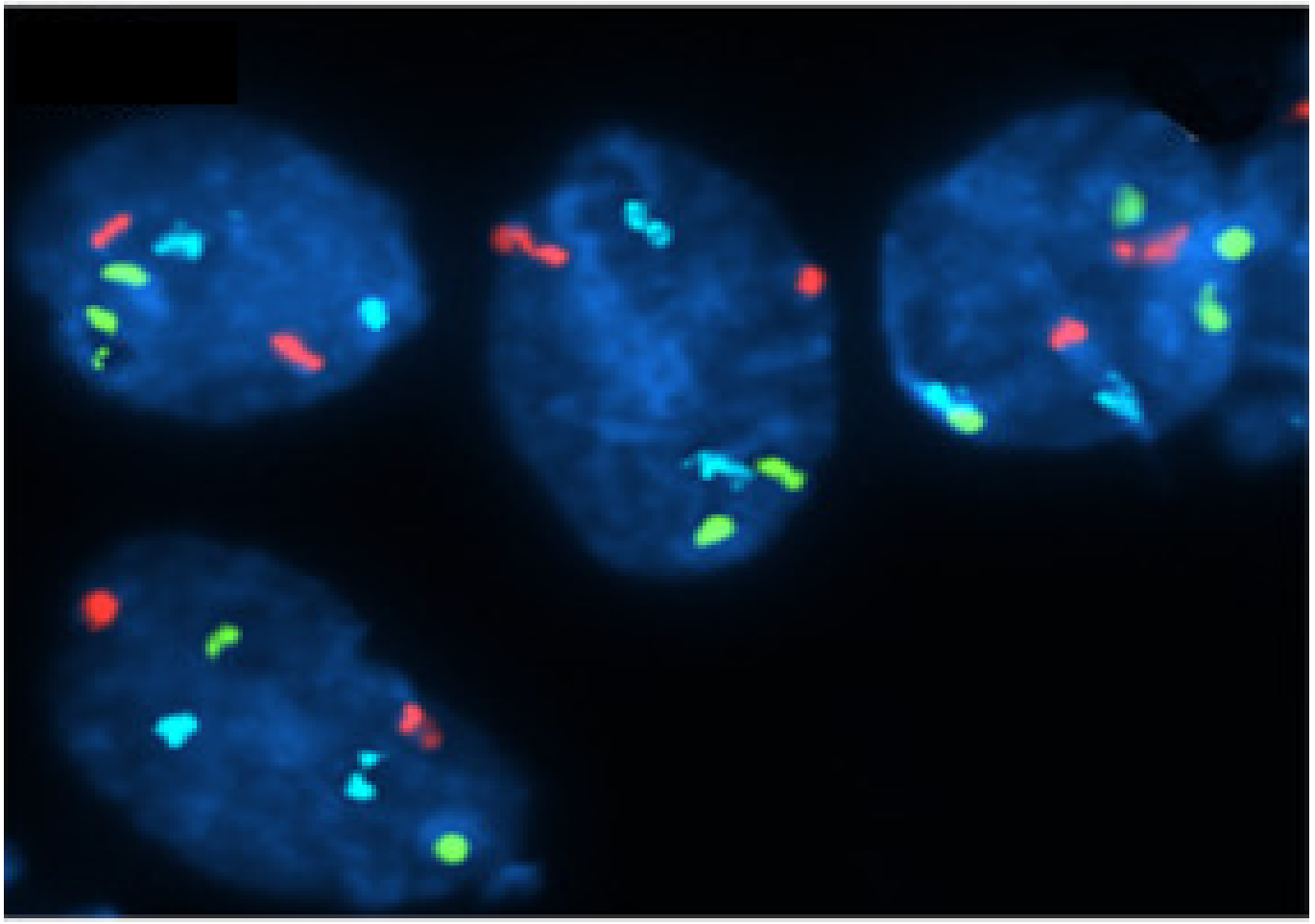
FISH



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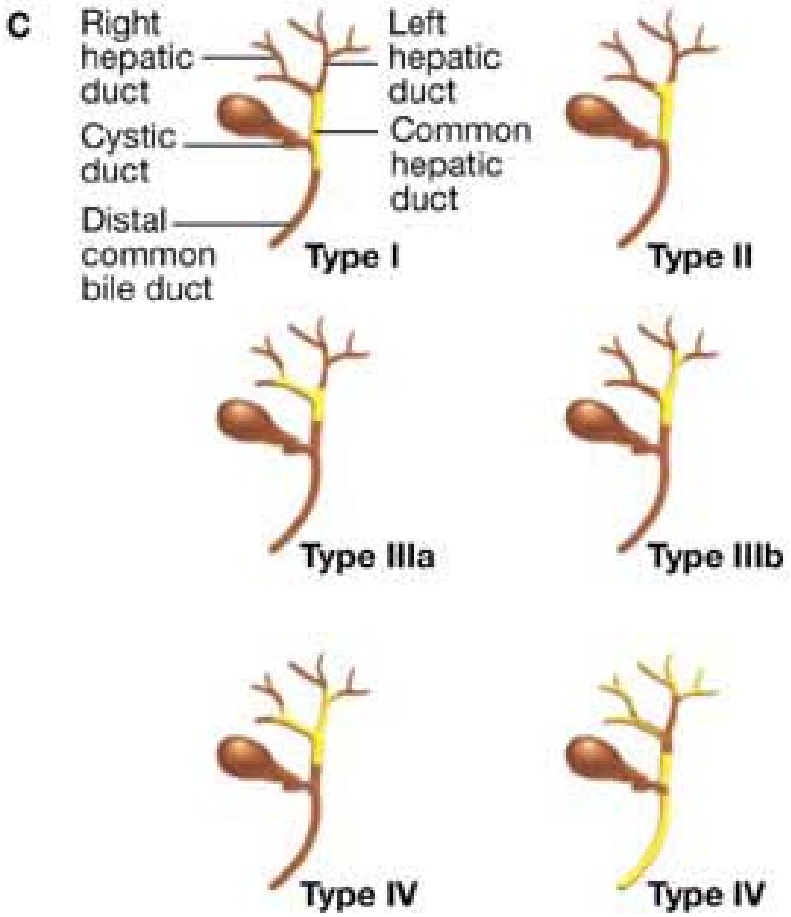
Staging

- evaluate location and extent of disease
- general guidelines for operability include:
  - absence of lymph node or liver metastases
  - absence of invasion of the portal vein
  - absence of direct invasion of adjacent organs
  - absence of widespread metastatic disease

Bismuth-Corlette Staging



Surgical Resection

- candidates without cirrhosis have classically undergone bile duct resection with or without hepatic resection
- the recent success of Liver Transplant for CCA has put this practice under some scrutiny

Surgery for CCA

- surgery offers only durable chance for cure
- during laparoscopy, 25% - 30% of patients who were thought to be candidates for surgical resection will be found to have unresectable CCA
- 15%–20% of CCA patients with unremarkable abdominal imaging studies have metastatic lymph node involvement on EUS evaluation

Prometheus

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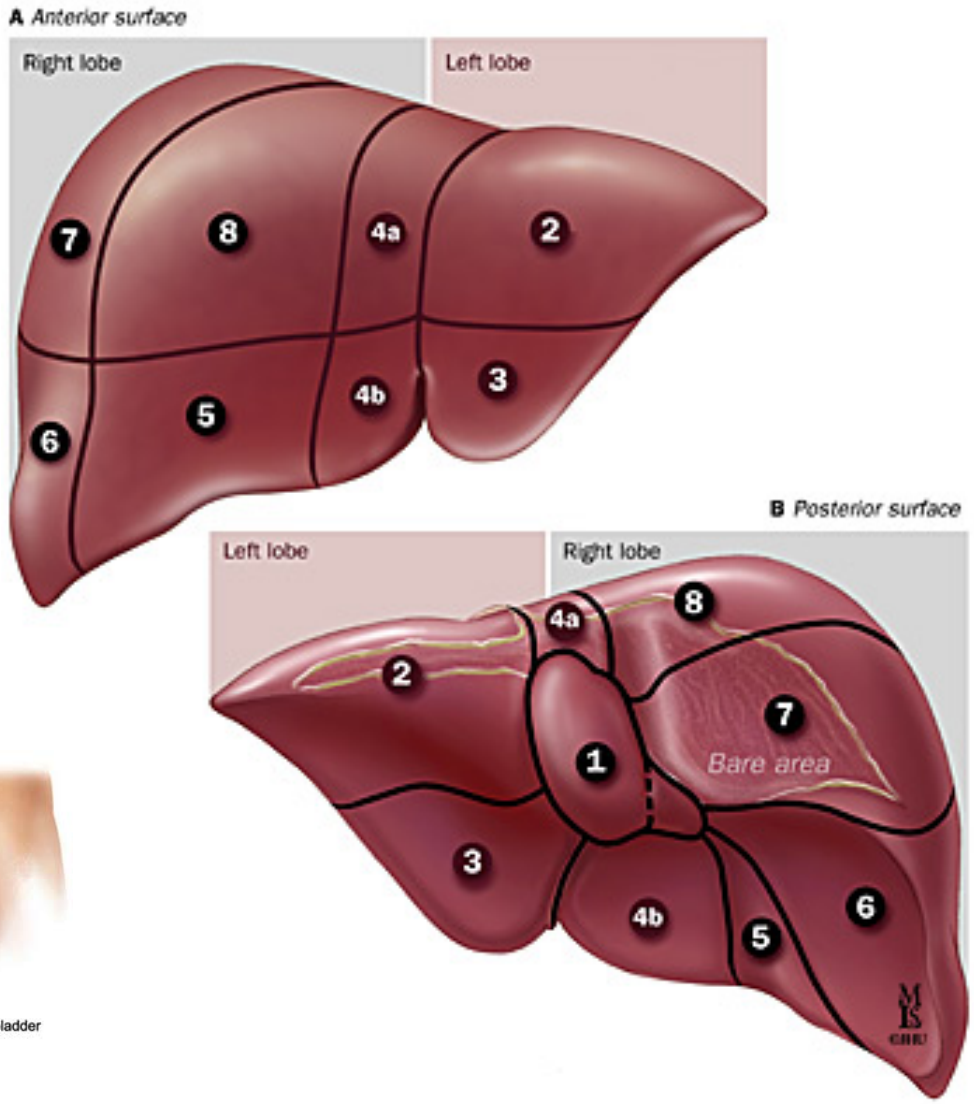
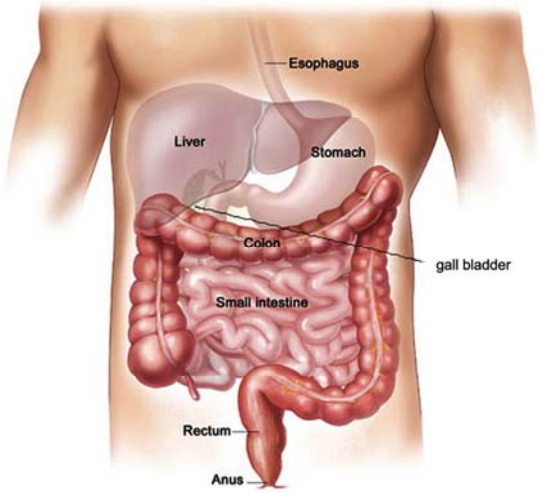
Prometheus Bound

According to Greek mythology, when the Olympian god Zeus hid fire from mortals, the Titan deity Prometheus stole it from Zeus and retuned it to the mortals. This enraged Zeus, who then had Prometheus taken to the Caucasus Mountains and bound naked to a rock. Every morning a vulture came and pecked away at Prometheus' liver. Each night, though, Prometheus' liver regenerated.


A Anterior surface
Right lobe
Left lobe
7
8
4a
2
6
5
4b
3
B Posterior surface
Left lobe
Right lobe
4a
8
2
7
1
Bare area
3
4b
5
6


Esophagus
Liver
Stomach
Colon
gall bladder
Small intestine
Rectum
Anus

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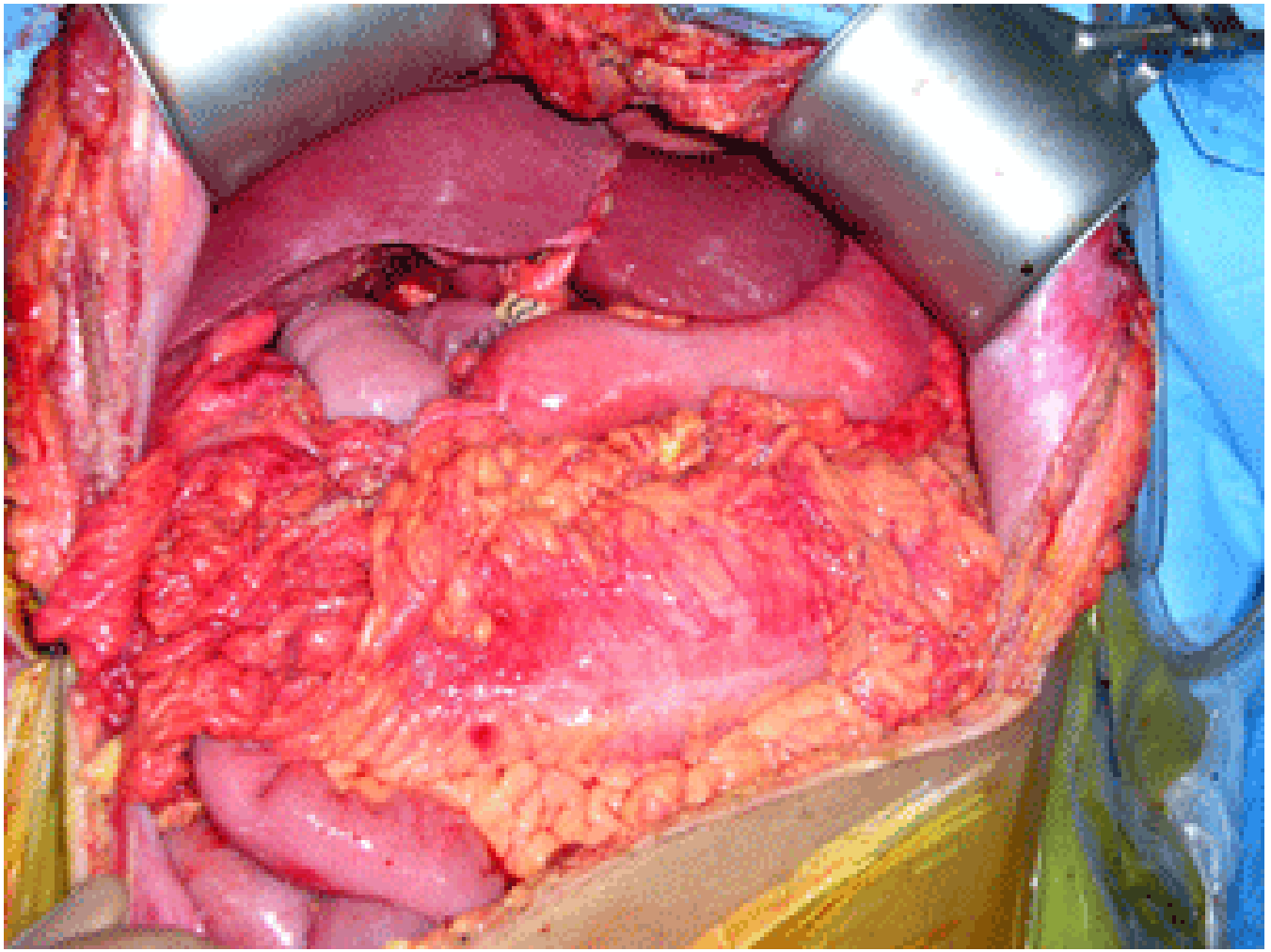

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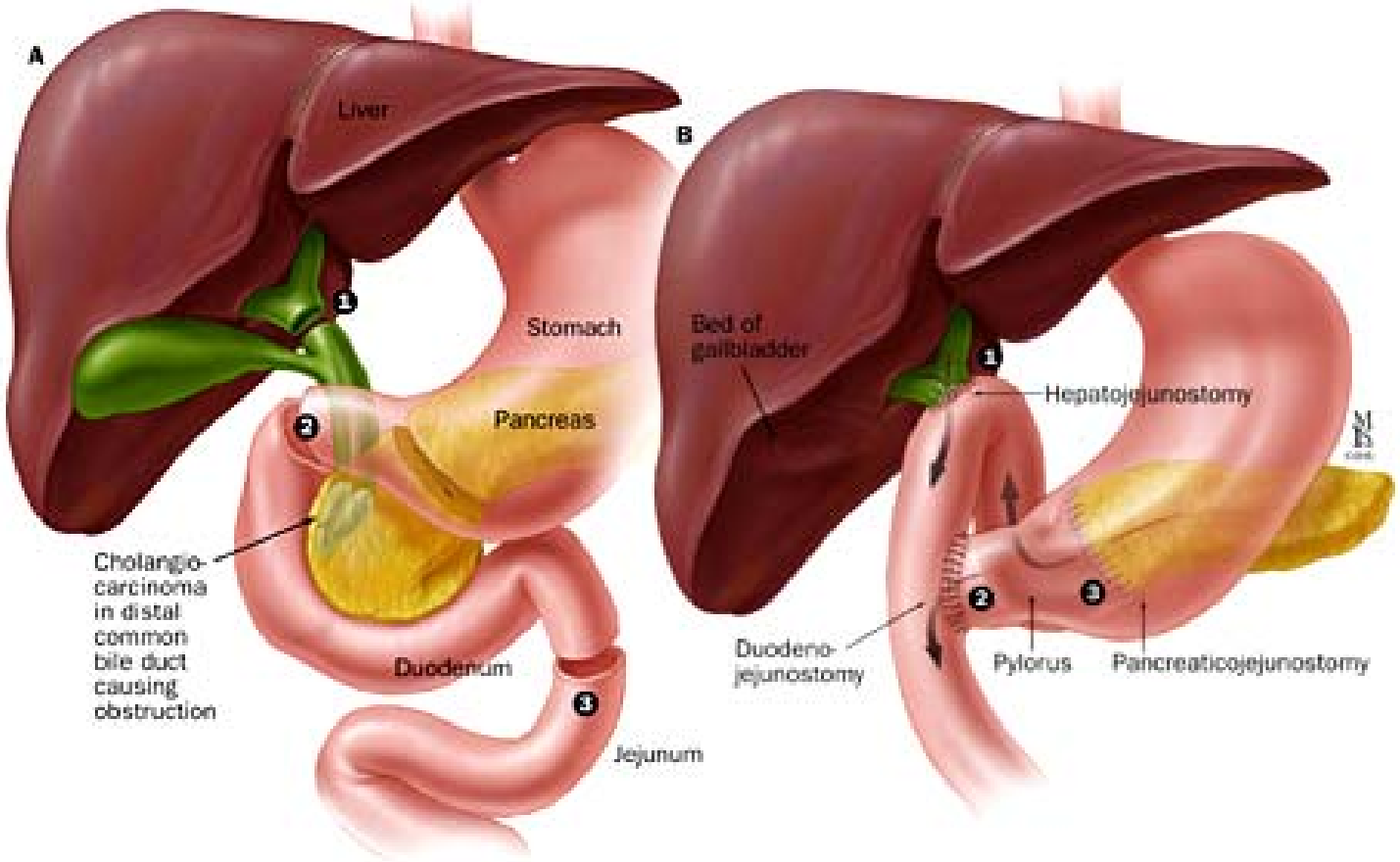
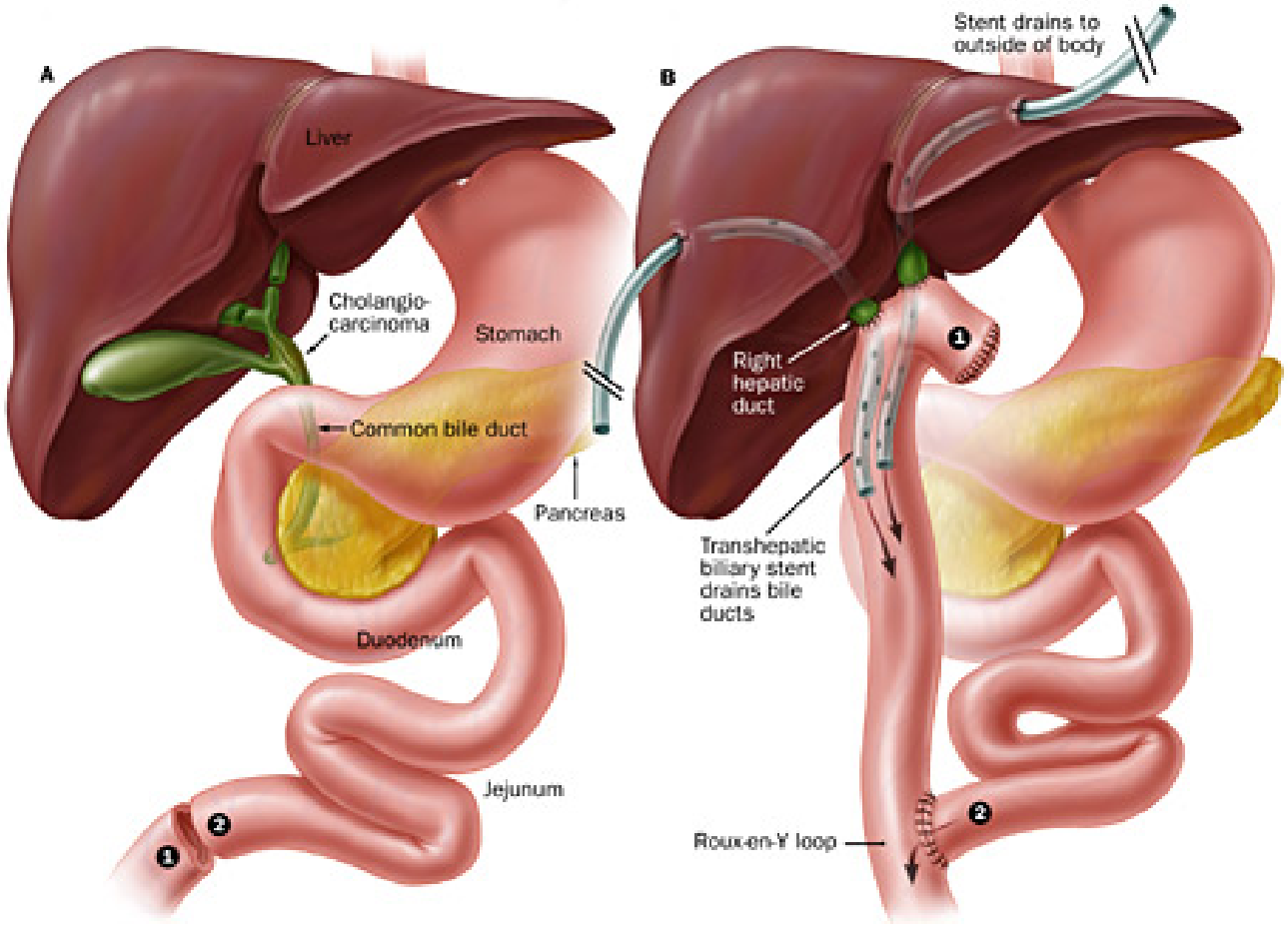
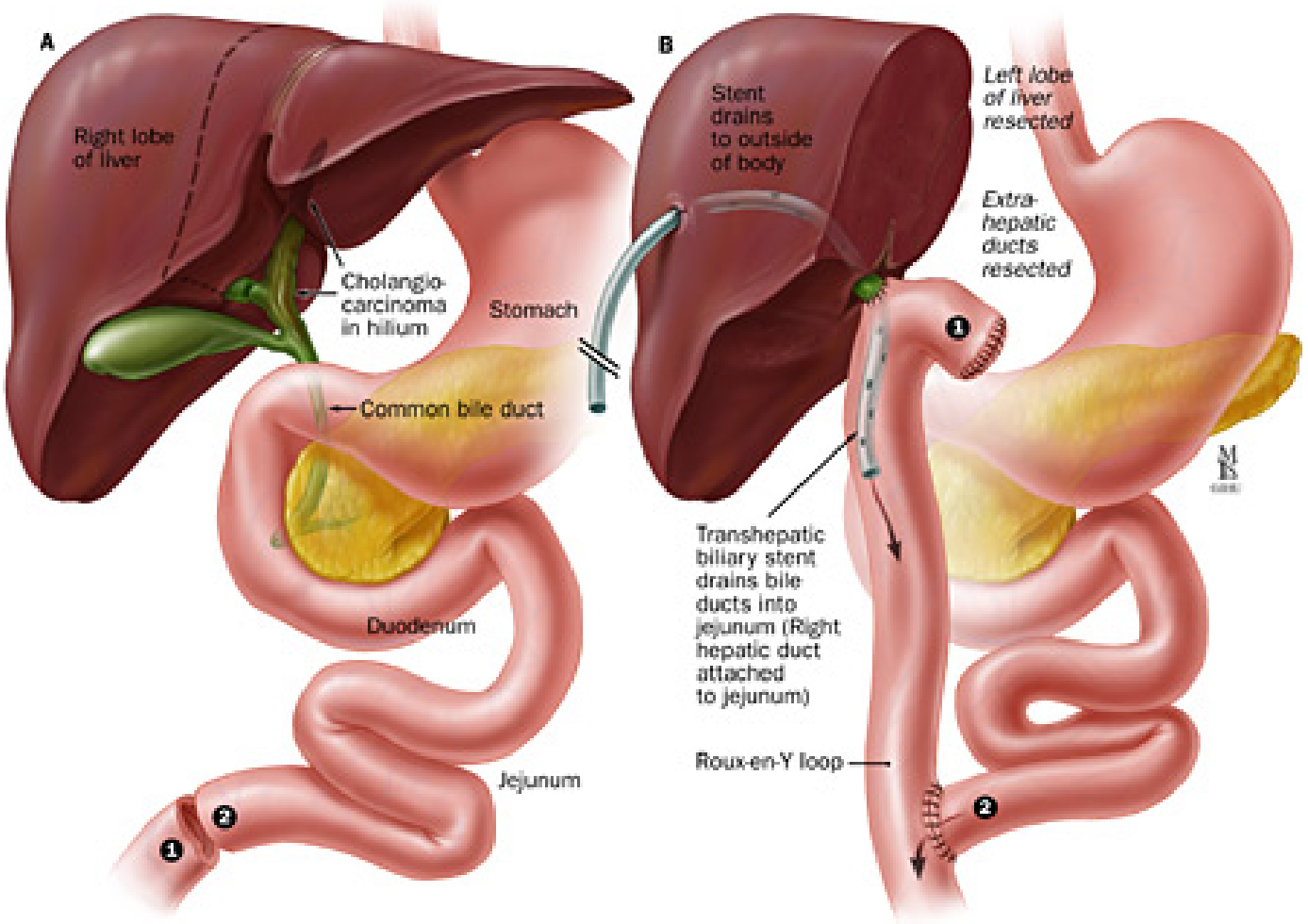

A
Liver
Stomach
Pancreas
Cholangio-
carcinoma
in distal
common
bile duct
causing
obstruction
Duodenum
Jejunum
B
Bed of
gallbladder
Hepatojejunostomy
Duodeno-
jejunostomy
Pylorus
Pancreaticojejunostomy

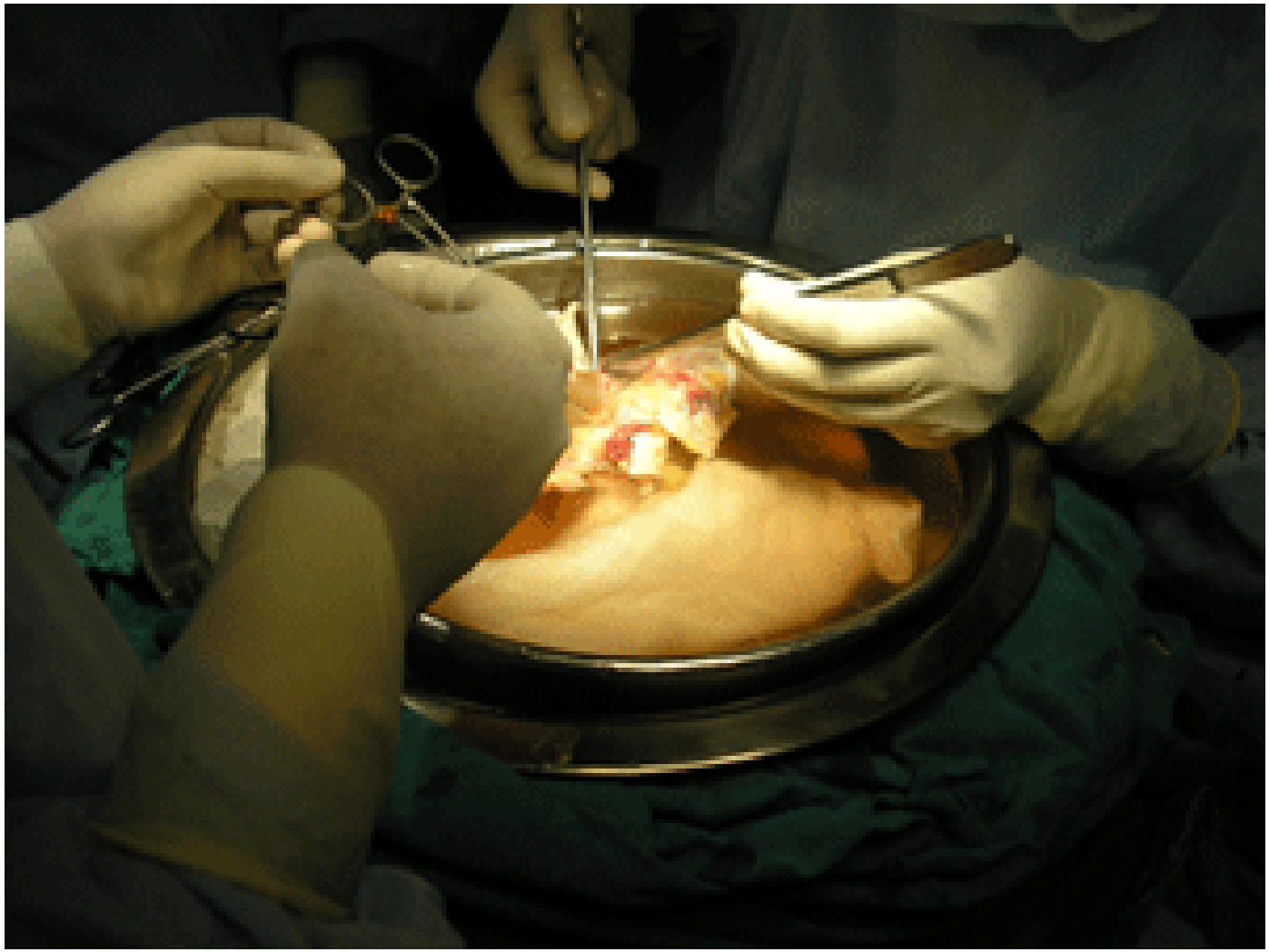

A
Liver
Cholangio-
carcinoma
Stomach
Common bile duct
Pancreas
Duodenum
Jejunum
1
2
B
Stent drains to
outside of body
Right
hepatic
duct
Transhepatic
biliary stent
drains bile
ducts
1
2
Roux-en-Y loop


A
Right lobe of liver
Cholangio-carcinoma in hilium
Stomach
Common bile duct
Duodenum
Jejunum
1
2
B
Stent drains to outside of body
Left lobe of liver resected
Extra-hepatic ducts resected
Transhepatic biliary stent drains bile ducts into jejunum (Right hepatic duct attached to jejunum)
Roux-en-Y loop
1
2

Prognosis

- not good
- without resection
  - median survival of 6 months
- with resection
  - 5-year survival of 20 – 40%


53



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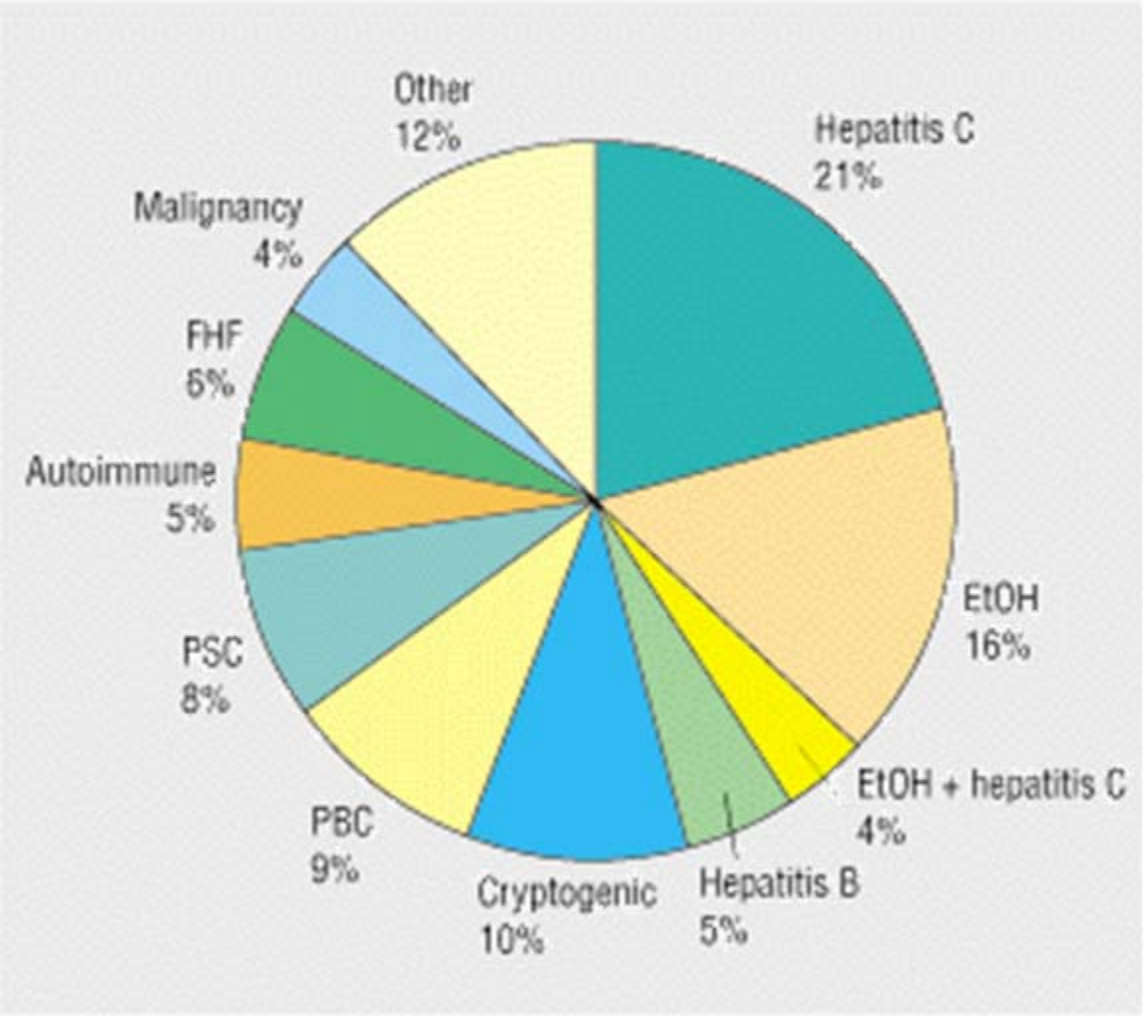
Indications for Liver Transplantation in the US



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Multi-Modality Approach to Therapy

External beam radiation therapy

Brachytherapy

Protracted venous infusion of 5-FU

Abdominal exploration for staging

Liver Transplantation

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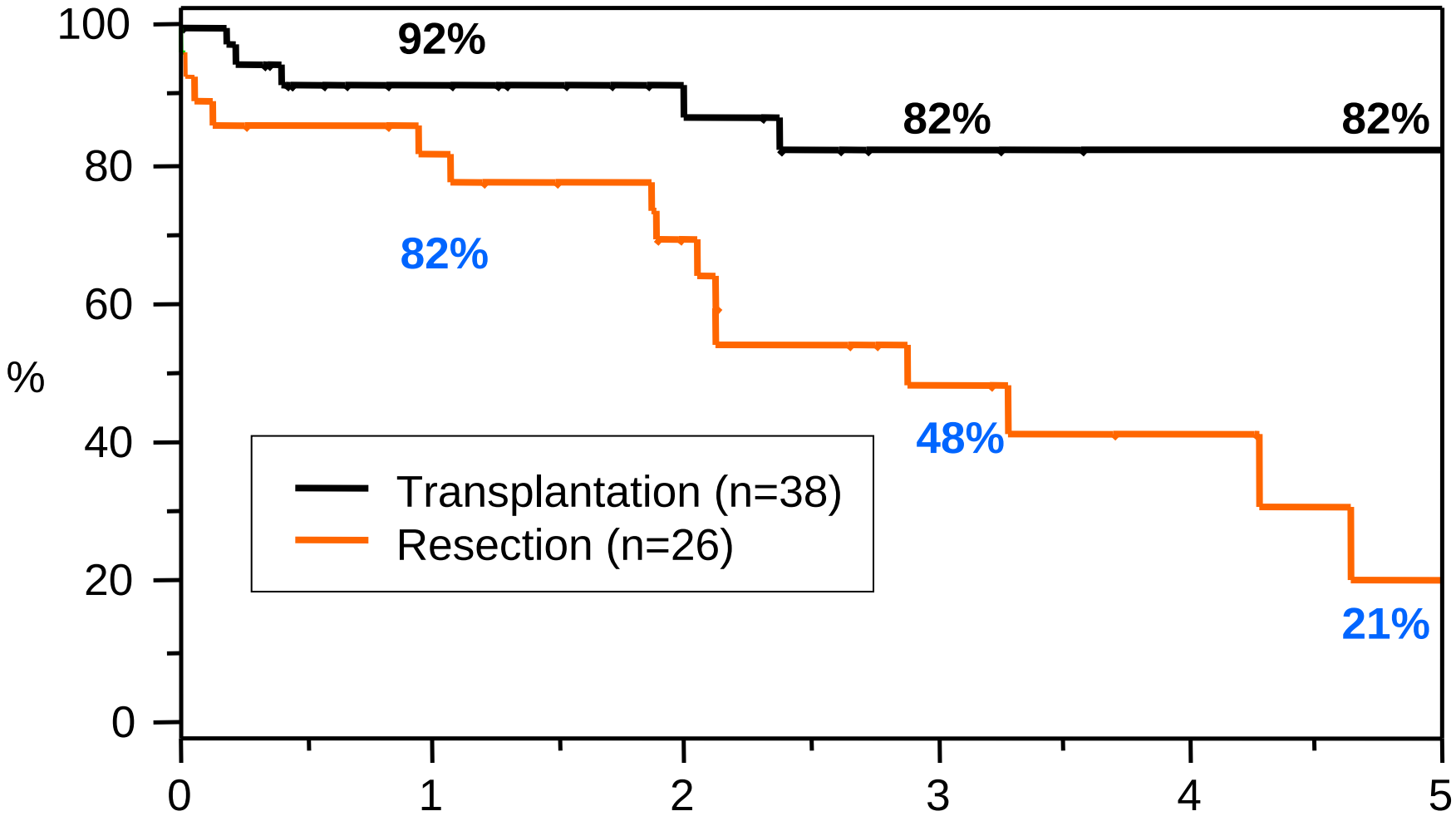
Results for CCA



ASA 2005

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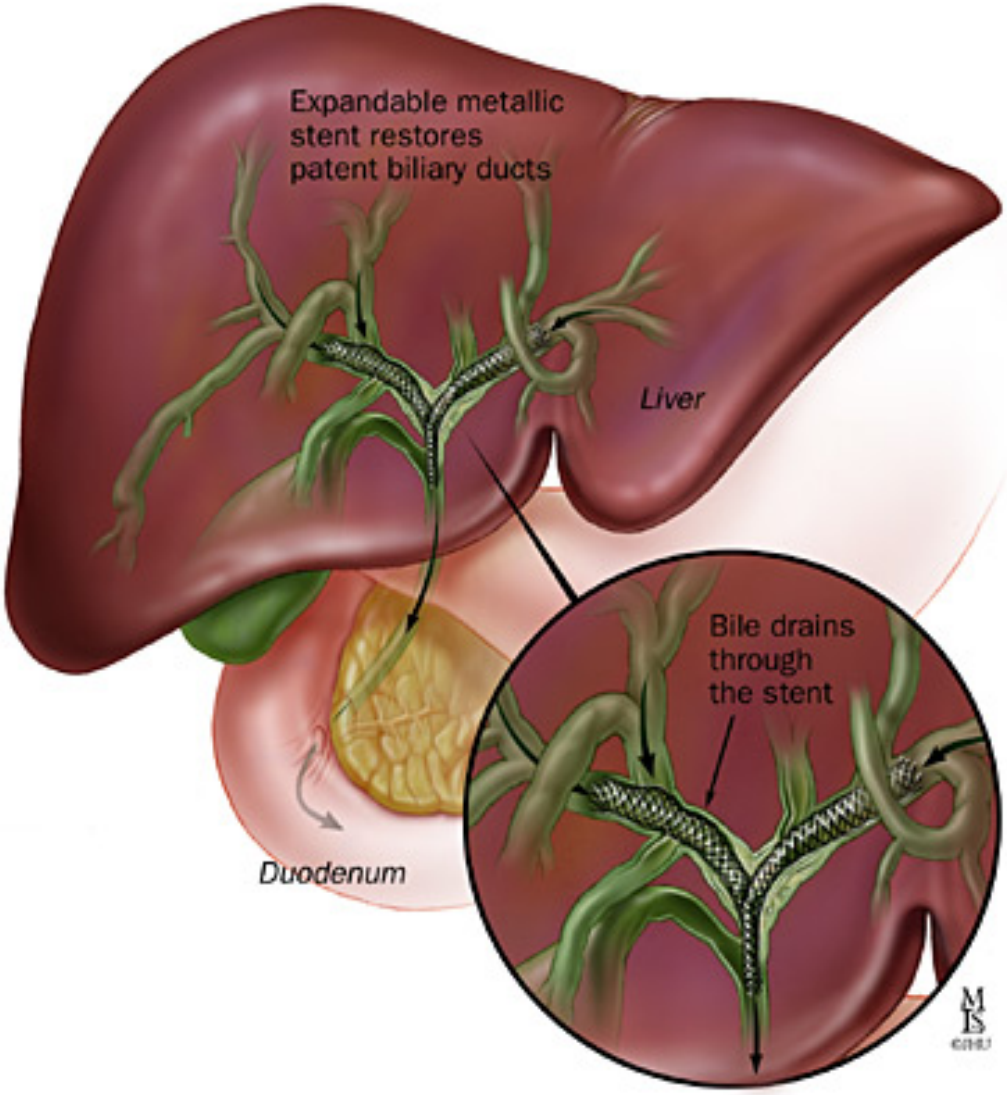
Palliative Therapy

- plays a major role in the mgmt of those with CCA
  - biliary stents
    - percutaneous
    - endoscopic
      - silastic
      - metal
  - photodynamic therapy
  - intraluminal brachytherapy
  - local ablative therapy


Expandable metallic stent restores patent biliary ducts
Liver
Bile drains through the stent
Duodenum

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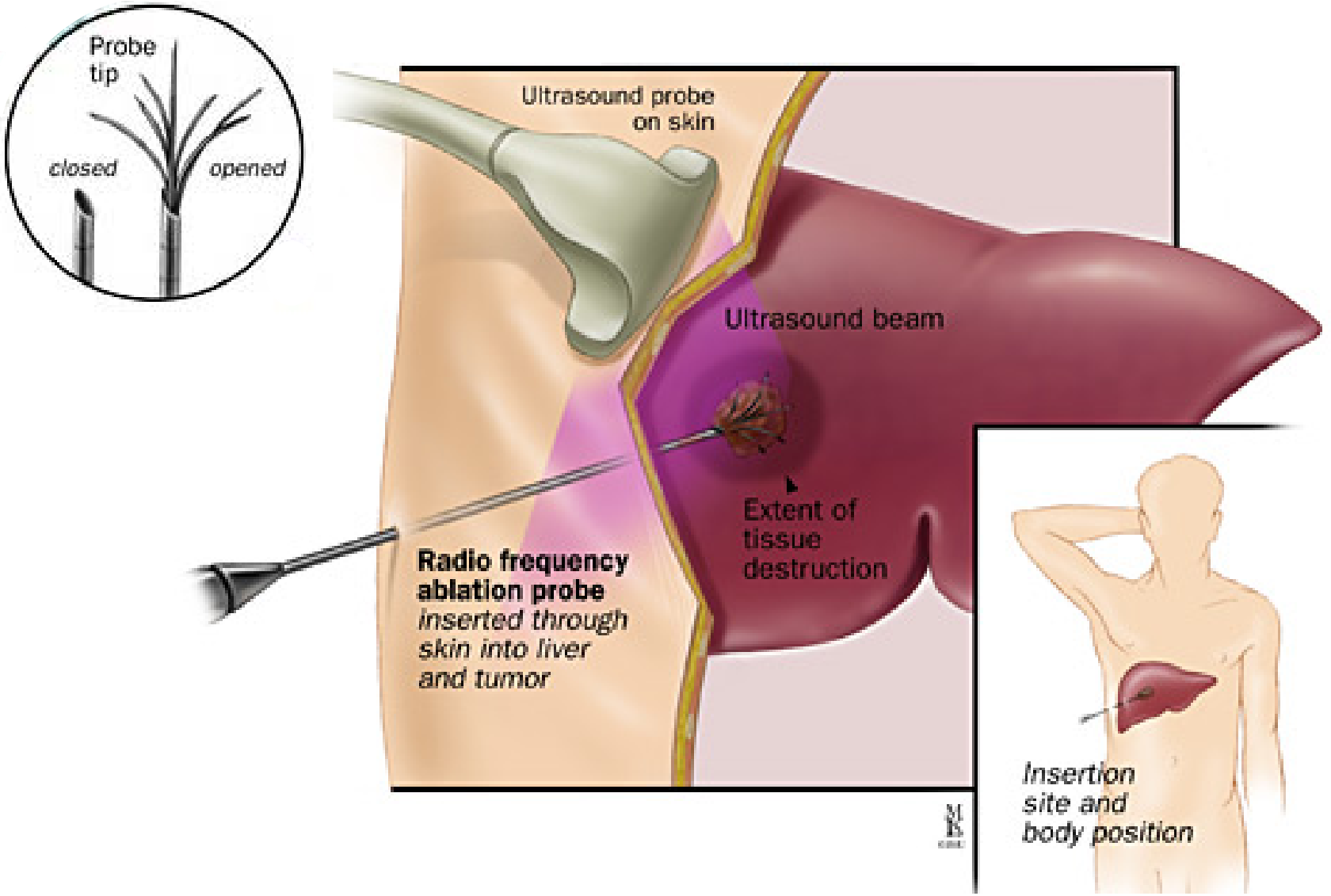
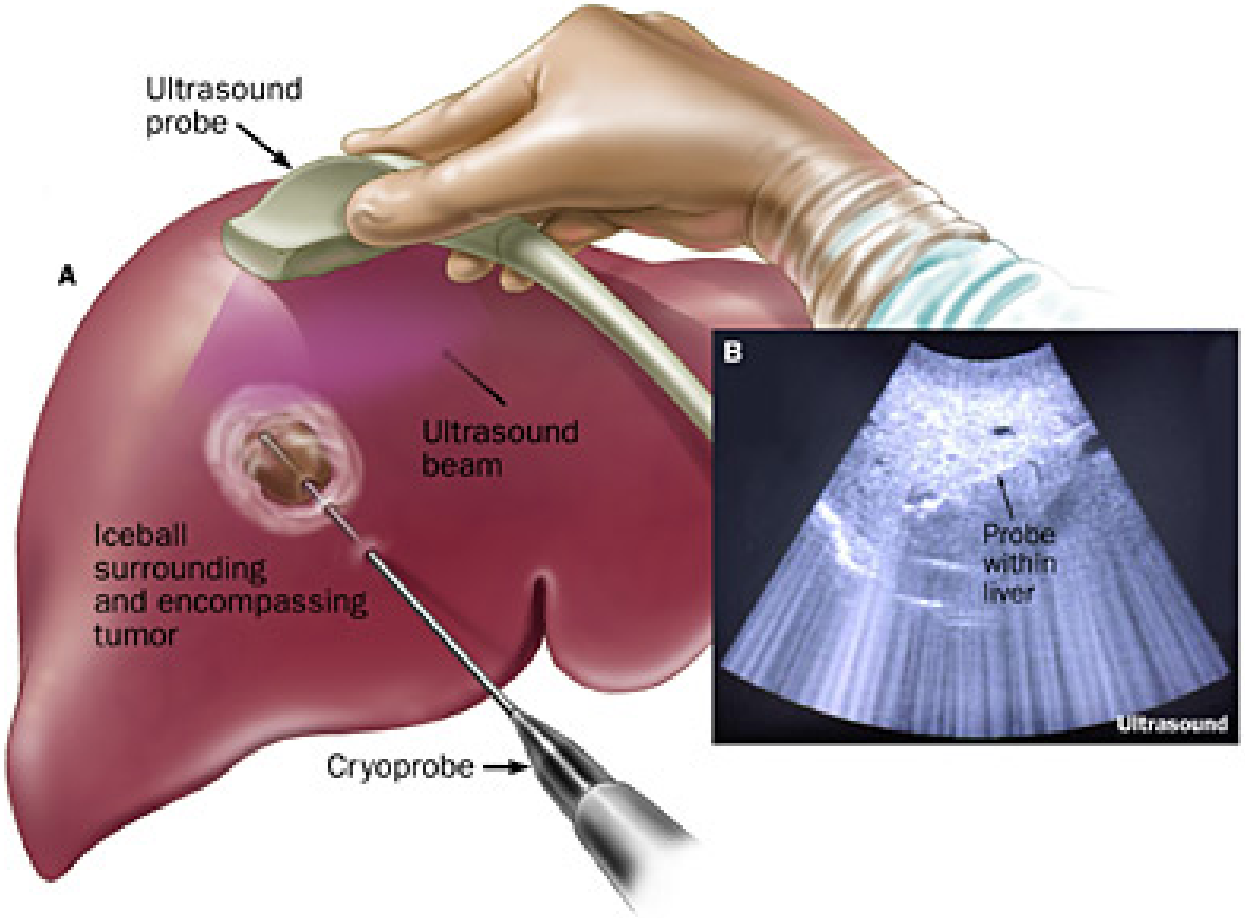

Probe tip
closed
opened
Ultrasound probe on skin
Ultrasound beam
Extent of tissue destruction
Radio frequency ablation probe
inserted through skin into liver and tumor
Insertion site and body position


Ultrasound probe
A
Ultrasound beam
Iceball surrounding and encompassing tumor
Cryoprobe
B
Probe within liver
Ultrasound

Common ChemoRx

113-cis-Retinoic Acid
22-CdA 2-Chlorodeoxyadenosine
55-Azacitidine 5-Fluorouracil 5-FU
66-Mercaptopurine 6-MP 6-TG 6-Thioguanine
AAbraxane Accutane ® Actinomycin-D Adriamycin ® Adrucil ® Agrylin ® Ala-Cort ® Aldesleukin Alemtuzumab ALIMTA Alitretinoin Alkaban-AQ ® Alkeran ® All-transretinoic Acid Alpha Interferon Altretamine Amethopterin Amifostine Aminoglutethimide Anagrelide Anandron ® Anastrozole Arabinosylcytosine Ara-C Aranesp ® Aredia ® Arimidex ® Aromasin ® Arranon ® Arsenic Trioxide Asparaginase ATRA Avastin ® Azacitidine
BBCG BCNU Bevacizumab Bexarotene BEXXAR ® Bicalutamide BiCNU Blenoxane ® Bleomycin Bortezomib Busulfan Busulfex ®
CC225 Calcium Leucovorin Campath ® Camptosar ® Camptothecin-11 Capecitabine Carac ™ Carboplatin Carmustine Carmustine Wafer Casodex ® CC-5013 CCI-779 CCNU CDDP CeeNU Cerubidine ® Cetuximab Chlorambucil Cisplatin Citrovorum Factor Cladribine Cortisone Cosmegen ® CPT-11 Cyclophosphamide Cytadren ® Cytarabine Cytarabine Liposomal Cytosar-U ® Cytoxan ®
DDacarbazine Dacogen Dactinomycin Darbepoetin Alfa Dasatinib Daunomycin Daunorubicin Daunorubicin Hydrochloride Daunorubicin Liposomal DaunoXome ® Decadron Decitabine Delta-Cortef ® Deltasone ® Denileukin diftitox DepoCyt ™ Dexamethasone Dexamethasone acetate Dexamethasone Sodium Phosphate Dexasone Dexrazoxane DHAD DIC Diodex Docetaxel Doxil ® Doxorubicin Doxorubicin liposomal Droxia ™ DTIC DTIC-Dome ® Duralone ®
EEfudex ® Eligard ™ Ellence ™ Eloxatin ™ Elspar ® Emcyt ® Epirubicin Epoetin alfa Erbitux ™ Erlotinib Erwinia L-asparaginase Estramustine Ethyol Etopophos ® Etoposide Etoposide Phosphate Eulexin ® Evista ® Exemestane
FFareston ® Faslodex ® Femara ® Filgrastim Floxuridine Fludara ® Fludarabine Fluoroplex ® Fluorouracil Fluorouracil (cream) Fluoxymesterone Flutamide Folinic Acid FUDR ® Fulvestrant
GG-CSF Gefitinib Gemcitabine Gemtuzumab ozogamicin Gemzar ® Gleevec ™ Gliadel ® Wafer GM-CSF Goserelin Granulocyte - Colony Stimulating Factor Granulocyte Macrophage Colony Stimulating Factor
HHalotestin ® Herceptin ® Hexadrol Hexalen ® Hexamethylmelamine HMM Hycamtin ® Hydrea ® Hydrocort Acetate ® Hydrocortisone Hydrocortisone Sodium Phosphate Hydrocortisone Sodium Succinate Hydrocortone Phosphate Hydroxyurea
IIbritumomab Ibritumomab Tiuxetan Idamycin ® Idarubicin Ifex ® IFN-alpha Ifosfamide IL-11 IL-2 Imatinib mesylate Imidazole Carboxamide Interferon alfa Interferon Alfa-2b (PEG Conjugate) Interleukin - 2 Interleukin-11 Intron A® (interferon alfa-2b) Iressa ® Irinotecan Isotretinoin
KKidrolase (t) Kidrolase ®
LLanacort ® Lapatinib L-asparaginase LCR Lenalidomide Letrozole Leucovorin Leukeran Leukine ™ Leuprolide Leurocristine Leustatin ™ Liposomal Ara-C Liquid Pred ® Lomustine L-PAM L-Sarcolysin Lupron ® Lupron Depot ®
MMatulane ® Maxidex Mechlorethamine Mechlorethamine Hydrochloride Medralone ® Medrol ® Megace ® Megestrol Megestrol Acetate Melphalan Mercaptopurine Mesna Mesnex ™ Methotrexate Methotrexate Sodium Methylprednisolone Meticorten ® Mitomycin Mitomycin-C Mitoxantrone M-Prednisol ® MTC MTX Mustargen ® Mustine Mutamycin ® Myleran ® Mylocel ™ Mylotarg ®
NNavelbine ® Nelarabine Neosar ® Neulasta ™ Neumega ® Neupogen ® Nexavar ® Nilandron ® Nilutamide Nipent ® Nitrogen Mustard Novaldex ® Novantrone ®
OOctreotide Octreotide acetate Oncospar ® Oncovin ® Ontak ® Onxal ™ Oprevelkin Orapred ® Orasone ® Oxaliplatin
PPaclitaxel Paclitaxel Protein-bound Pamidronate Panitumumab Panretin ® Paraplatin ® Pediapred ® PEG Interferon Pegaspargase Pegfilgrastim PEG-INTRON ™ PEG-L-asparaginase PEMETREXED Pentostatin Phenylalanine Mustard Platinol ® Platinol-AQ ® Prednisolone Prednisone Prelone ® Procarbazine PROCRIT ® Proleukin ® Prolifeprospan 20 with Carmustine Implant Purinethol ®
RRaloxifene Revlimid ® Rheumatrex ® Rituxan ® Rituximab Roferon-A ® (Interferon Alfa-2a) Rubex ® Rubidomycin hydrochloride
SSandostatin ® Sandostatin LAR ® Sargramostim Solu-Cortef ® Solu-Medrol ® Sorafenib SPRYCEL ™ STI-571 Streptozocin SU11248 Sunitinib Sutent ®
TTamoxifen Tarceva ® Targretin ® Taxol ® Taxotere ® Temodar ® Temozolomide Temsirolimus Teniposide TESPA Thalidomide Thalomid ® TheraCys ® Thioguanine Thioguanine Tabloid ® Thiophosphoamide Thioplex ® Thiotepa TICE ® Toposar ® Topotecan Toremifene Torisel ® Tositumomab Trastuzumab Tretinoin Trexall ™ Trisenox ® TSPA TYKERB ®
VVCR Vectibix ™ Velban ® Velcade ® VePesid ® Vesanoid ® Viadur ™ Vidaza ® Vinblastine Vinblastine Sulfate Vincasar Pfs ® Vincristine Vinorelbine Vinorelbine tartrate VLB VM-26 Vorinostat VP-16 Vumon ®
XXeloda ®
ZZanosar ® Zevalin ™ Zinecard ® Zoladex ® Zoledronic acid Zolinza Zometa ®

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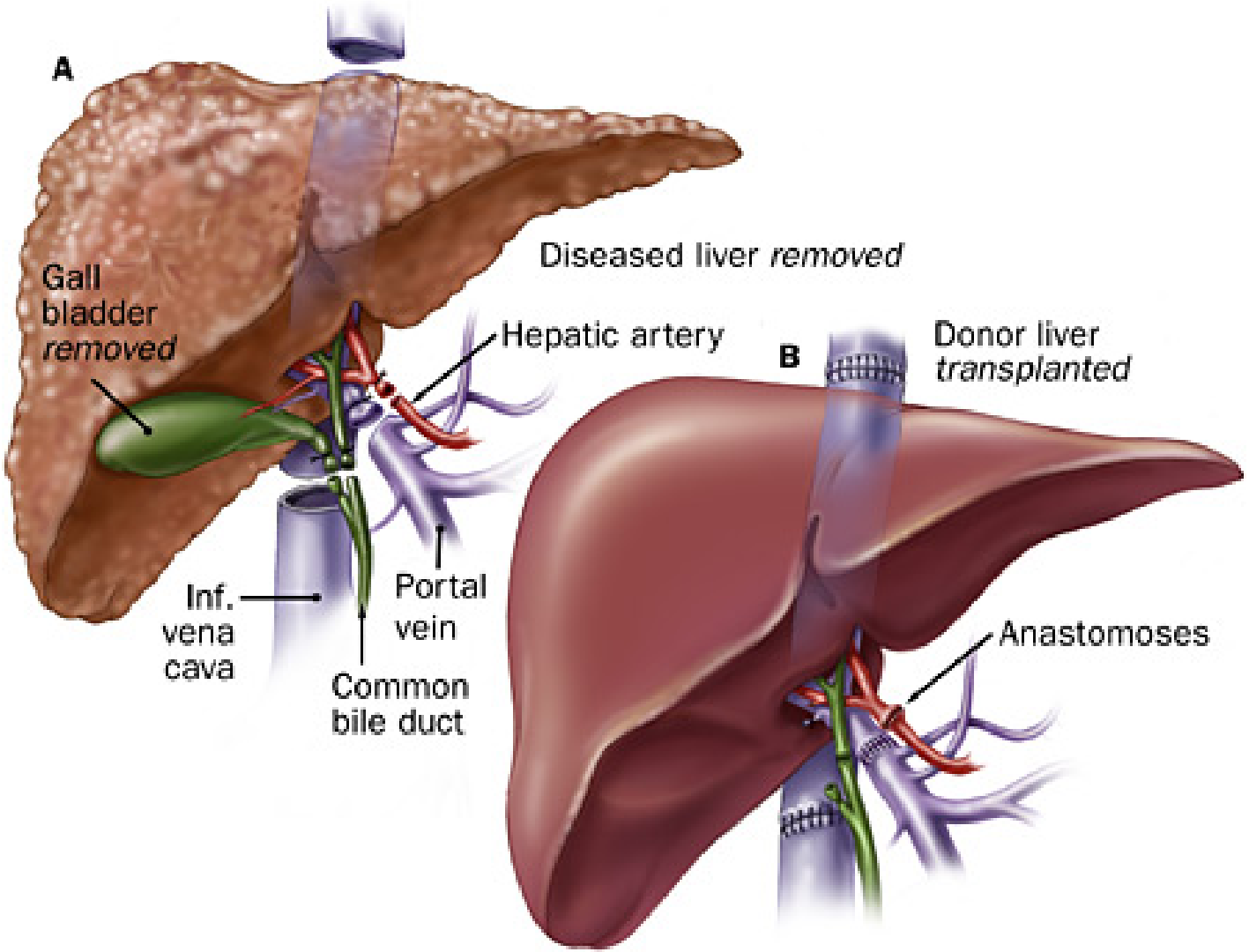
Future CCA Therapy

- high-intensity intraductal ultrasound
- intra-operative radiation therapy
- chemotherapeutic regimen combinations

Transplantation for PSC

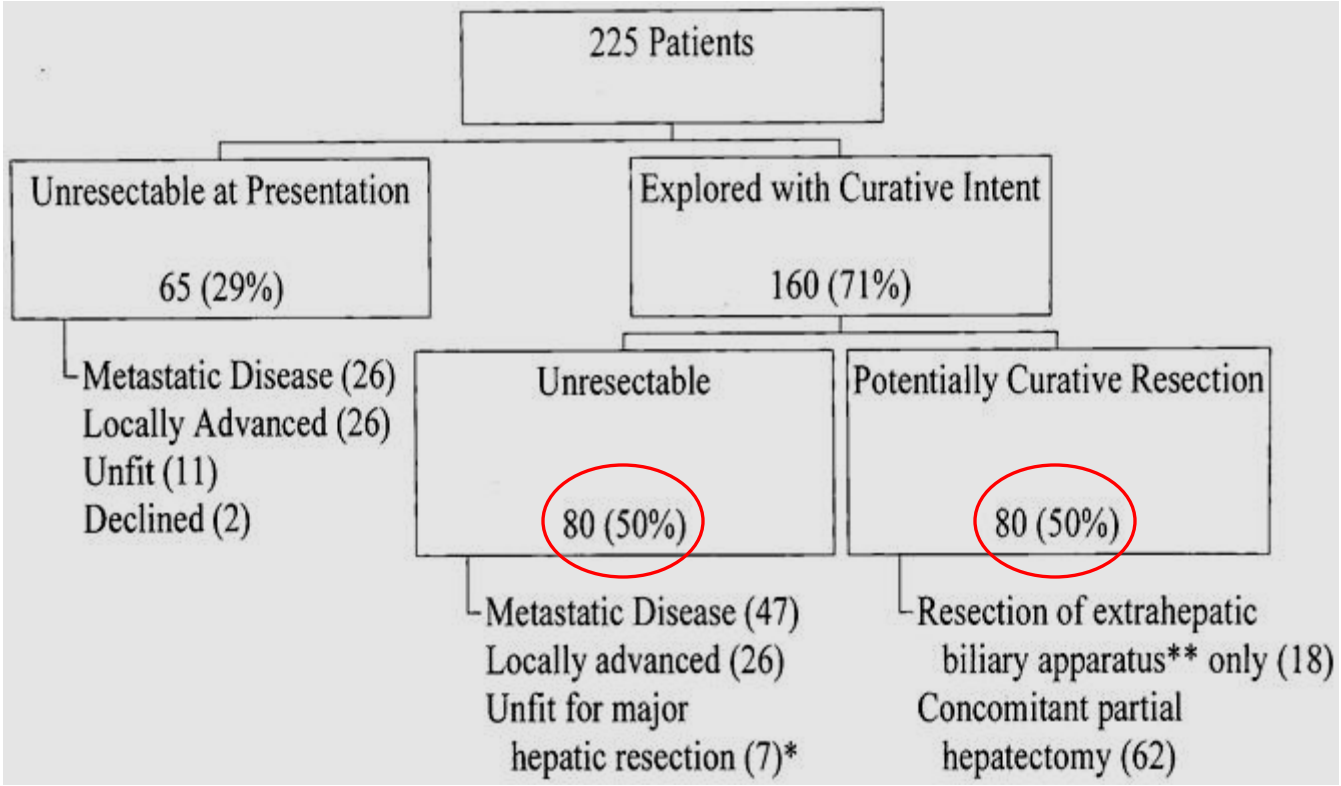
- OLT remains the only established long-term treatment for PSC
- long-term results are excellent
- 1-year survival at 90%
- recurrence of PSC in the liver graft is a particular problem and affects as many as 20–40% long-term


A
Gall bladder *removed*
Diseased liver *removed*
Hepatic artery
Inf. vena cava
Portal vein
Common bile duct
B
Donor liver *transplanted*
Anastomoses

Summary

- PSC remains a disease that is progressive and treatment is less than ideal
- surgery has a role in treating PSC complications, CCA and cirrhosis
- outcome after Liver Transplantation is excellent (better for non-CCA)

Questions?



Flow diagram showing the results of the initial investigation and surgical findings of all patients in the series. *Seven patients were judged unfit for extended hepatic resection, two because of unexpected cirrhosis and five because of significant underlying coronary artery disease. **Resection of supraduodenal bile duct, cholecystectomy, subhilar lymphadenectomy. +Twenty-three patients had distant metastases (liver, peritoneal cavity, lung, or bone), whereas three had disease in retroperitoneal lymph nodes. ++Twenty-five patients had metastases to N2-level lymph nodes and 22 had distant disease (9 to the liver, 9 to the peritoneum, and 4 to liver and peritoneum).

Ann Surg. 2001 October; 234(4): 507–519. **Staging, Resectability, and Outcome in 225 Patients With Hilar Cholangiocarcinoma**
William R. Jarnagin, MD, et al. Memorial Sloan-Kettering Cancer Center, New York, New York

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Table 3. HISTOPATHOLOGIC FEATURES OF RESECTED TUMORS, PERIOPERATIVE RESULTS, AND SURVIVAL

	All Resections (n = 80)	Hepatic Resection (n = 62)	No Hepatic Resection (n = 18)
Histopathology			
Negative margin	62 (78%)	52 (84%)*	10 (56%)*
Tumor size (cm)	2.2 ± 1.4	2.8 ± 1.5†	2 ± 0.8†
Tumor > 2.5 cm	30 (38%)	27 (44%)	3 (17%)
Well differentiated	30 (38%)	20 (32%)	10 (56%)
Node positive	19 (24%)	16 (26%)	3 (17%)
Papillary tumor	14 (18%)	8 (13%)†	6 (33%)†
Perioperative Results			
Estimated blood loss (mL)			
Mean ± SD	978 ± 940	1,045 ± 850	622 ± 366
Median (range)	800 (130–7,000)	850 (130–7,000)	450 (300–1,200)
Number (%) transfused	37 (46%)	32 (52%)	5 (28%)
Total units transfused			
Mean ± SD	4.8 ± 12	5.3 ± 13	2.7 ± 7
Median (range)	1 (0–71)	2 (0–71)	0 (0–25)
Hospital stay (days)			
Mean ± SD	15 ± 8	15 ± 7	13 ± 8
Median (range)	13 (6–49)	14 (6–49)	12 (7–37)
Complications	51 patients (64%)	42 patients (68%)	9 patients (50%)
Surgical deaths	8 (10%)	7 (11%)	1 (6%)
Survival			
Median (mo)	35	46§	26§
5-year (actuarial)	27%	37%	0%
5-year (actual)	30% (9/30 at risk)	39% (9/23 at risk)	0% (0/7 at risk)

Survival calculations include the perioperative deaths.
* $P < .01$.
† $P < .05$.
‡ $P < .04$.