ΗΚΚ & ΧΚΚ & Μεταστατική νόσος ήπατος

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Ακαδημαϊκός Υπότροφος

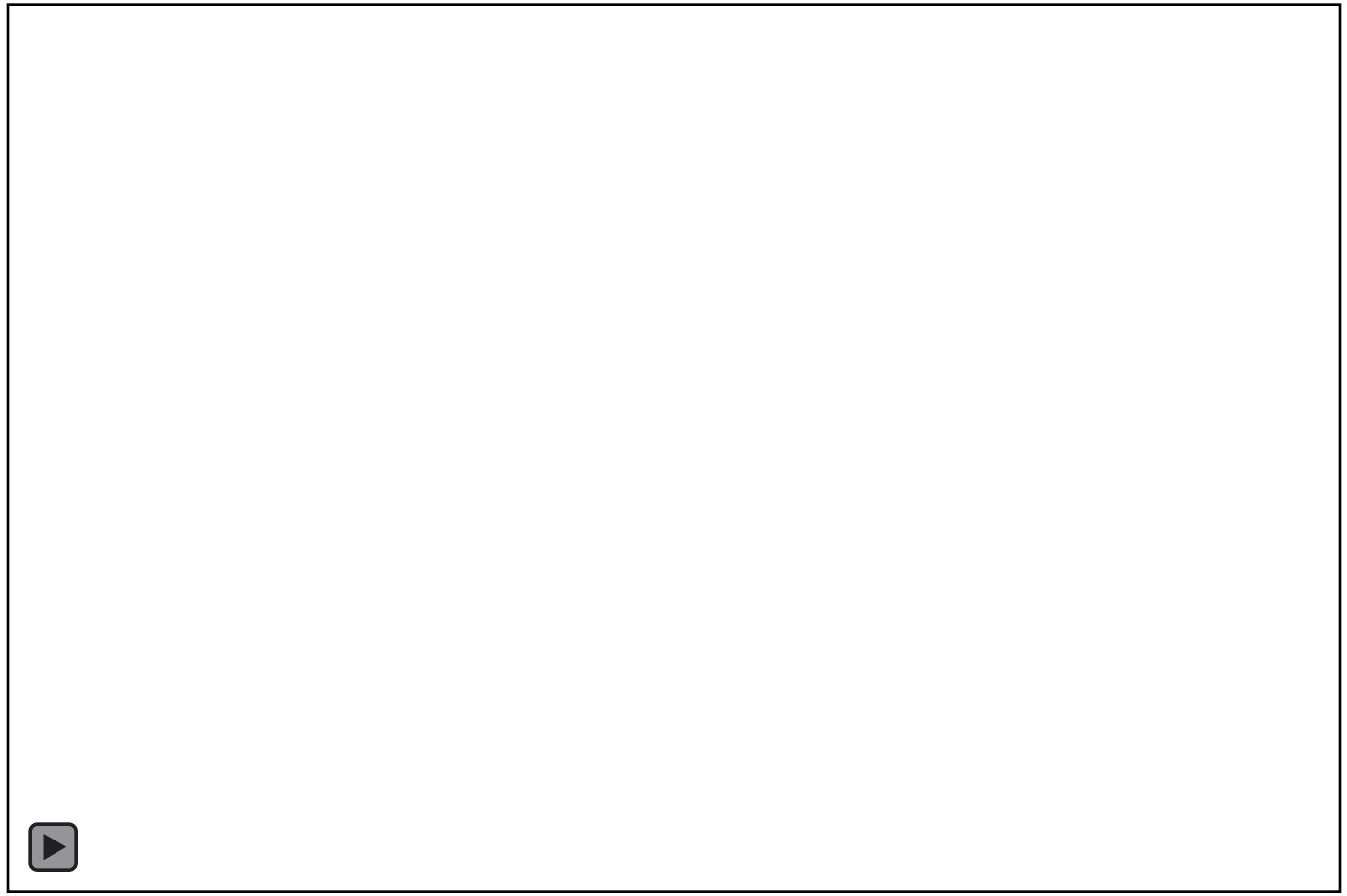
Α΄ Χειρουργική Κλινική ΕΚΠΑ

ΛΑΪΚΟ
ΓΕΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ ΑΘΗΝΩΝ
ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ

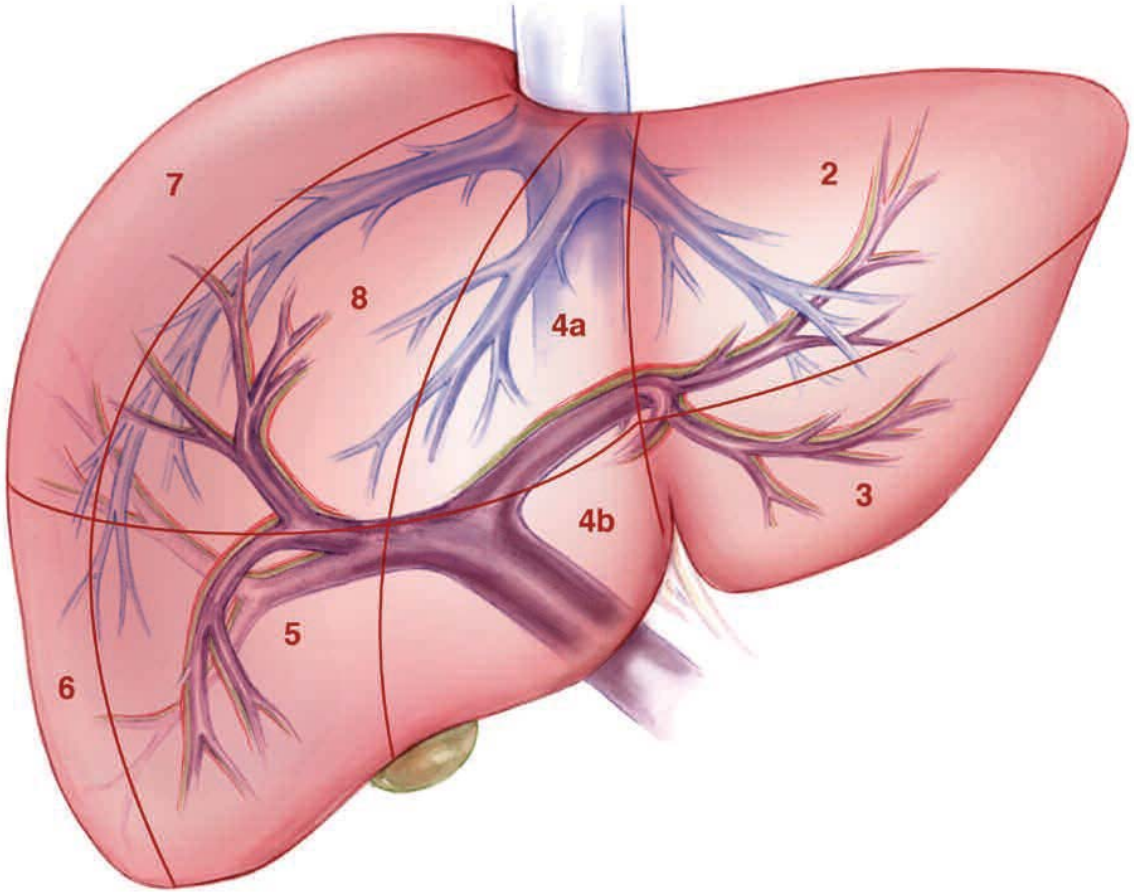
Σύγκρουση συμφερόντων εγκύκλιος ΕΟΦ (Αρ. Πρωτ. 47558/04-07-2012)

- Ουδεμία

Liver anatomy



Liver anatomy



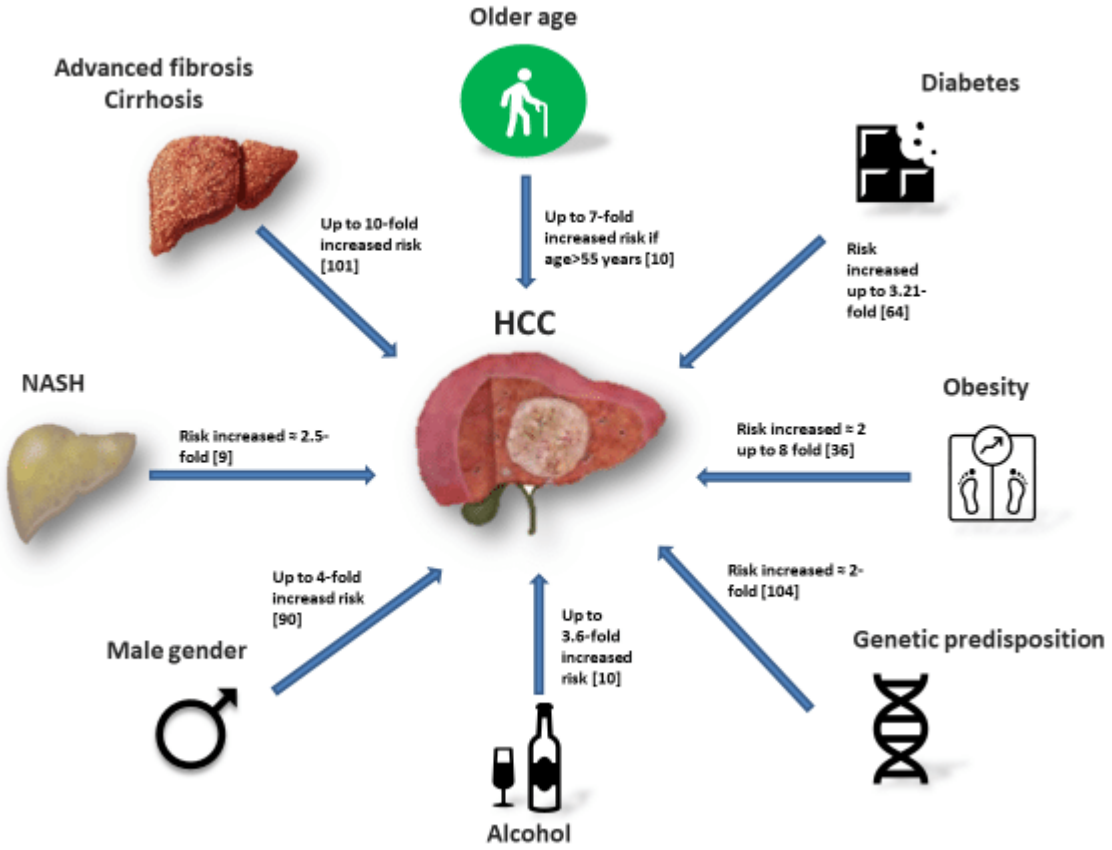
HCC

- the incidence of HCC is greatest in areas where exposure to factors that cause chronic HCC injury is heaviest.

- greatest in sub-Saharan Africa and East Asia, where the incidence is more than 20 cases per 100,000 individuals per year

- males have up to 5.7 times the HCC incidence observed in females

Risk factors for HCC



- 75% to 80% of primary liver tumours are associated with hepatitis B (seen in 50%-55% of patients with HCC) or hepatitis C (25%-30%)

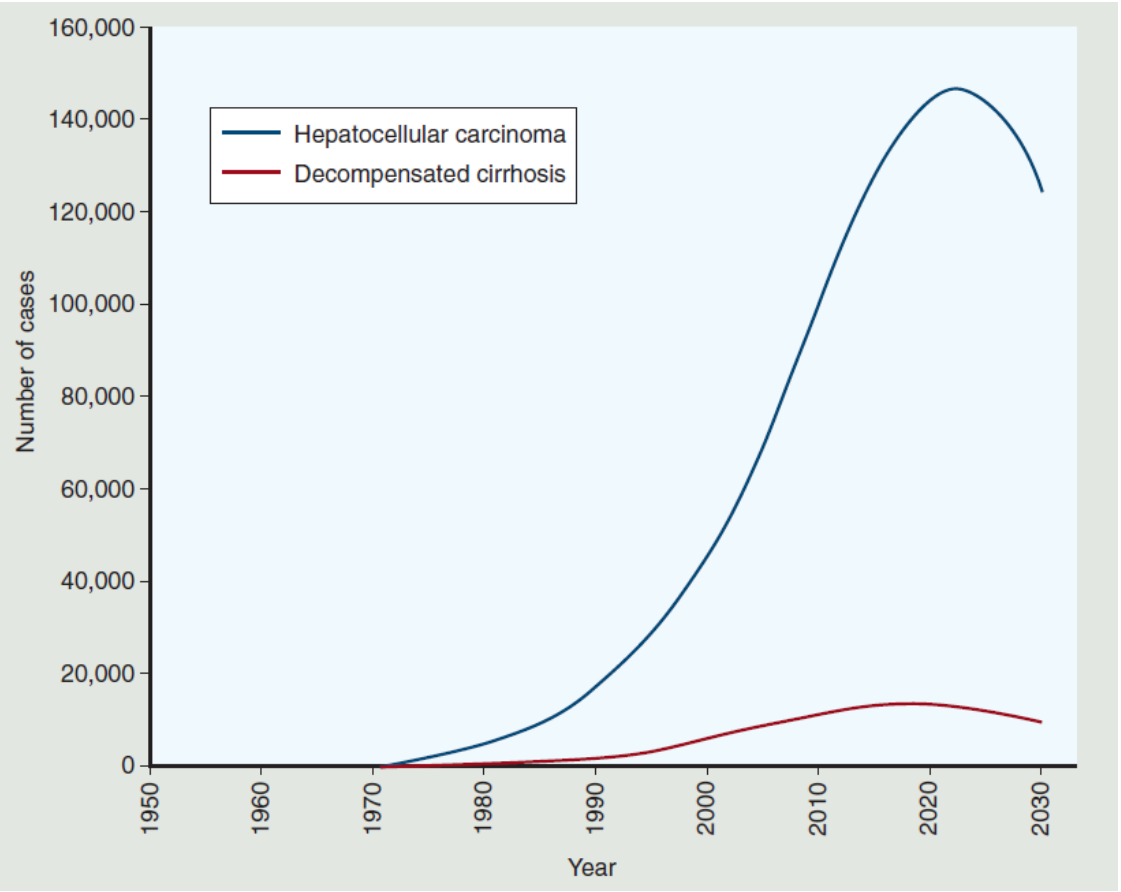
- Among patients with hepatitis B, 20% of HCC cases develop before cirrhosis develops, whereas among patients with hepatitis C, HCC almost always arises in the background of significant cirrhosis and fibrosis

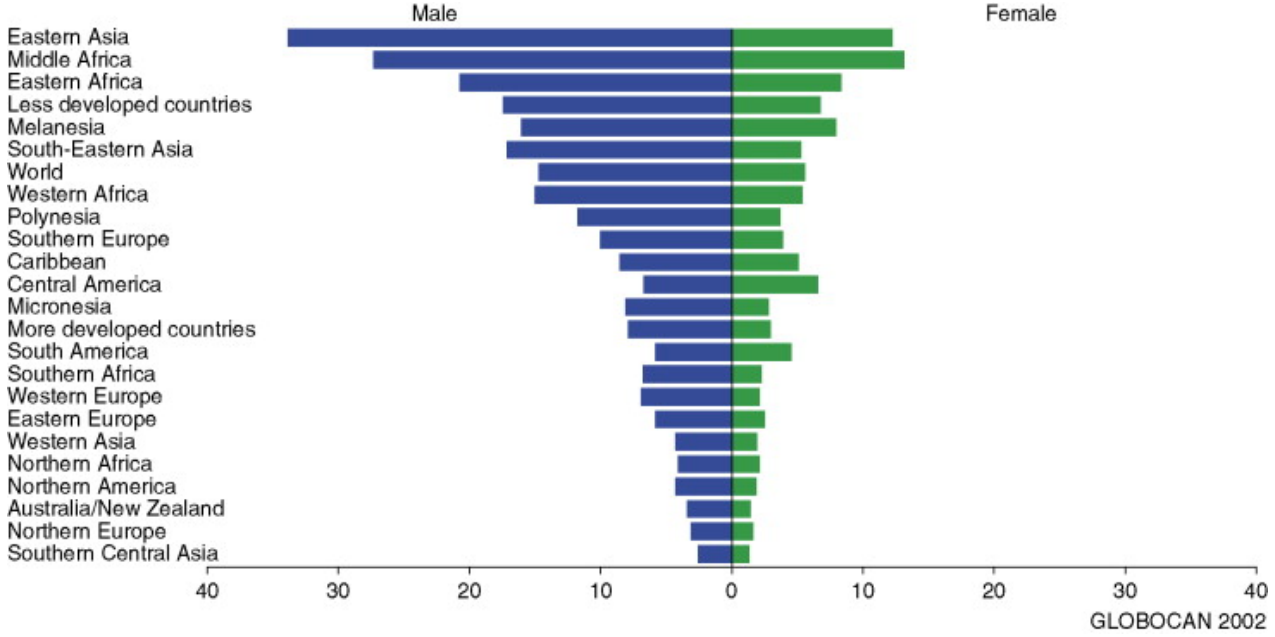
s B and better detection of

a revolution.

0% of patients with HCC are

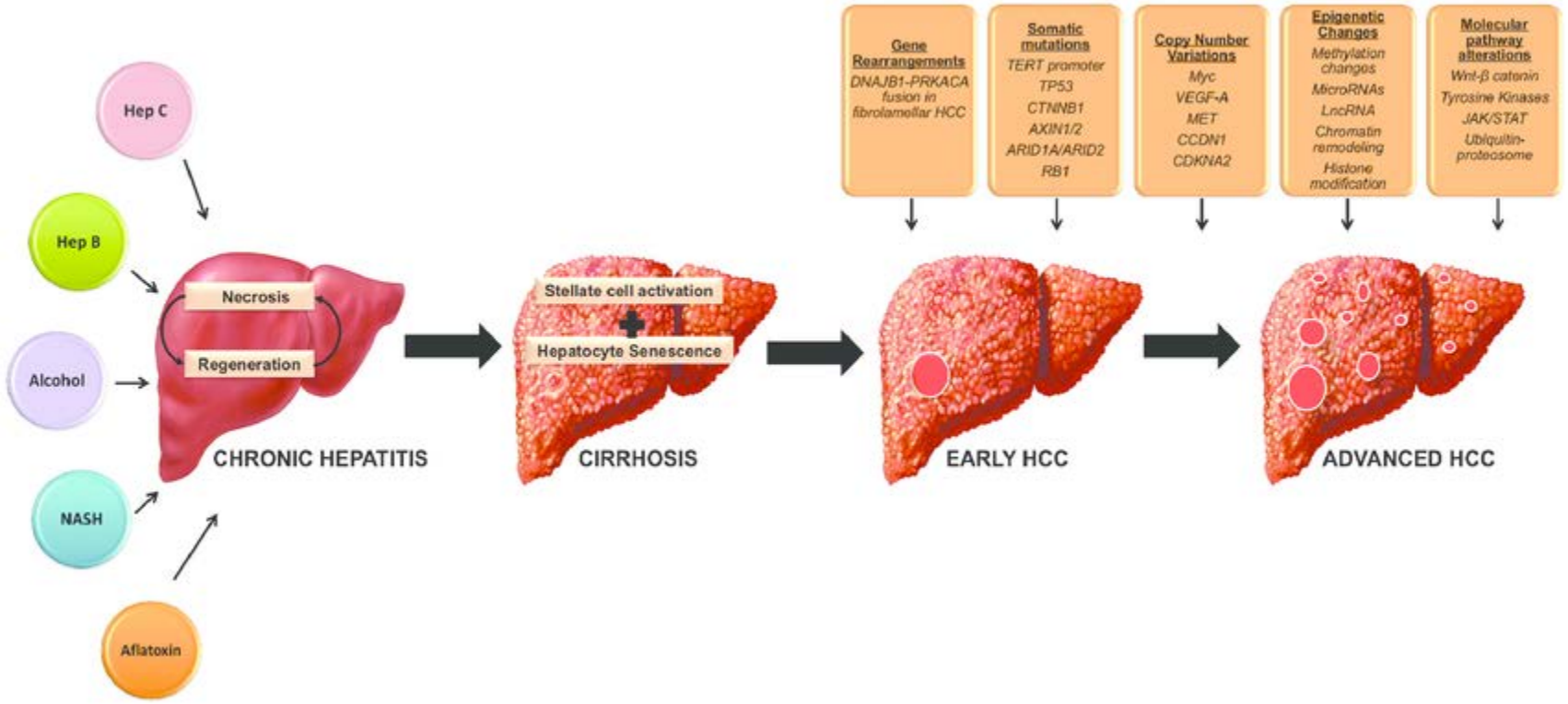
virus





Davis GL, Alter
MJ, El-Seraq H, Poynard T, Jennings LW. Aging of hepatitis C virus-infected persons in the United States: a multiple cohort model of
HCV prevalence and disease progression. *Gastroenterology*. 2010;138:513

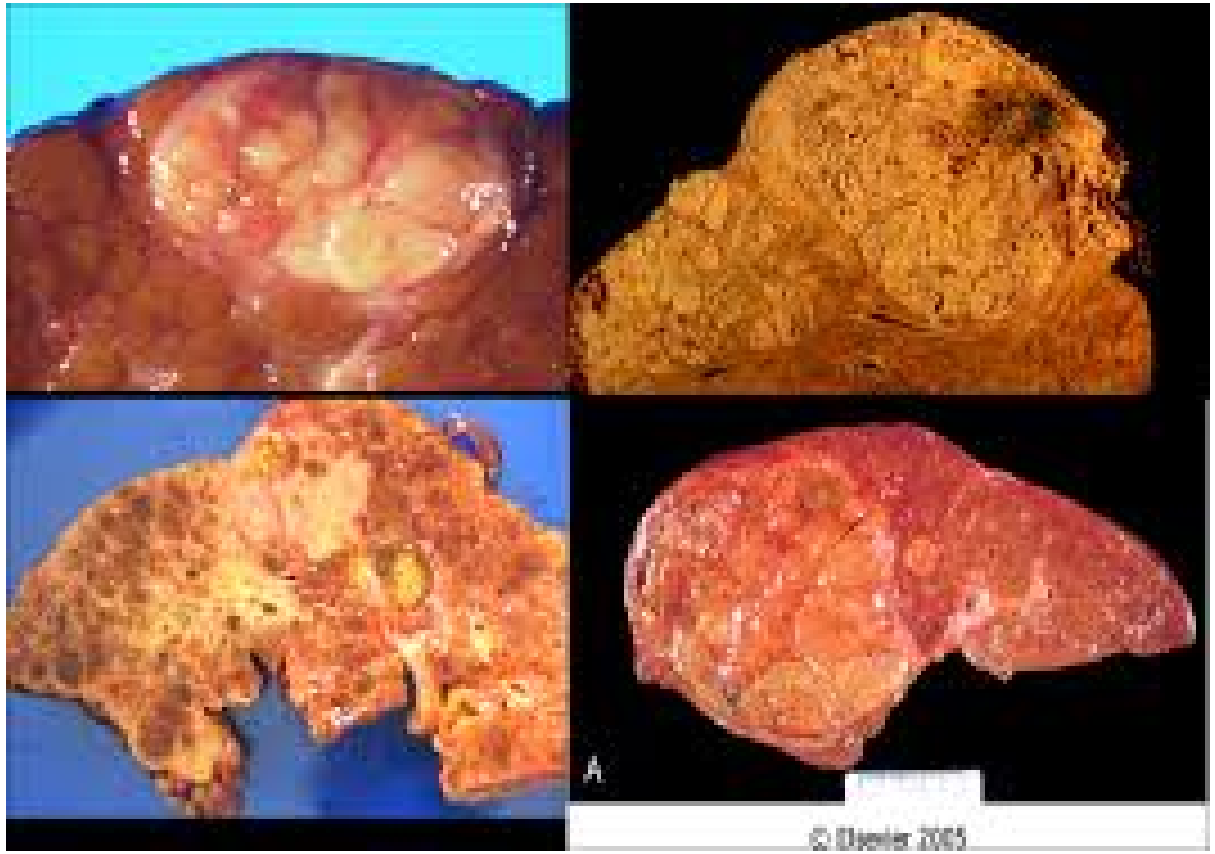
multistep progression through alterations in various molecular pathways



Gross features

Growth patterns categorized by Eggel

- nodular type
- massive
- diffuse

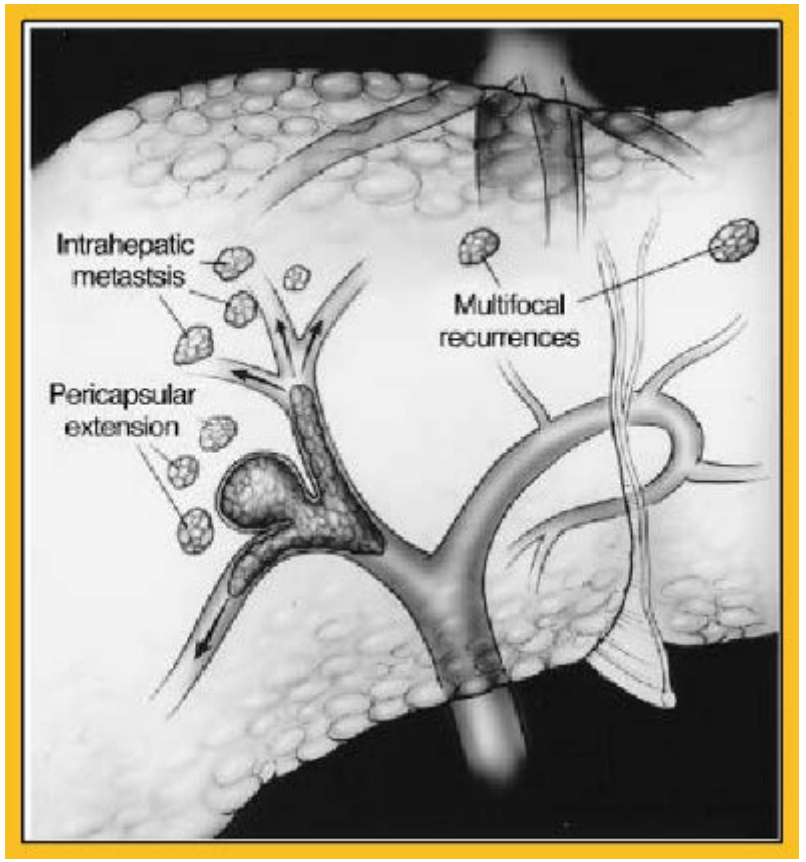


Clinical Presentation and Diagnosis

- often presents incidentally as patients are being followed for underlying liver disease or when there is enough tumor progression to cause a mass effect
- Right upper quadrant pain
- obstructive jaundice
- weight loss, anorexia, or onset of ascites
- rarely present as a rupture
- Physical examination is most often dominated by the signs of cirrhosis, such as jaundice, ascites, cachexia, splenomegaly, hepatomegaly, spider angiomata, or palmar erythema
- the physical exam may be normal in patients with HBV or NASH who can experience HCC prior to the development of cirrhosis.

PARANEOPLASTIC SYNDROMES ASSOCIATED WITH HEPATOCELLULAR CARCINOMA

Clinical Manifestation	Underlying Mechanism
Hypoglycemia	Increased metabolic activity Insulin-like growth factor II secretion
Hypercalcemia	Parathyroid hormone–related protein secretion
Watery diarrhea	Vasoactive intestinal polypeptide, gastrin, or prostaglandin activity
Hypercholesterolemia	Cholesterol dysregulation
Erythrocytosis	Erythropoietin secretion
Thrombocytopenia	Portal hypertension
Cutaneous	Cytokines secretion
Seborrheic keratoses	
Pityriasis rotunda	
Dermatomyositis	
Pemphigus foliaceus	
Porphyria cutanea tarda	



LABORATORY FINDINGS

- Abnormal liver function and elevated liver enzymes (ALT, AST, ALP, Bil, γ-GT)
- Viral serologies including hepatitis B surface antigen and hepatitis C antibody tests are also necessary
- Thrombocytopenia
- A-FP elevated (neither highly sensitive nor specific)
- up to 40% of patients with small HCCs have normal AFP levels
- can be elevated in patients with active viral hepatitis without cancer
- des-carboxyprothrombin (DCP) and the lens culinaris agglutinin-reactive fraction of AFP, termed AFP-L3, are candidate biomarkers that may increase the specificity for HCC when used with serum AFP screening.

Screening in high-risk population

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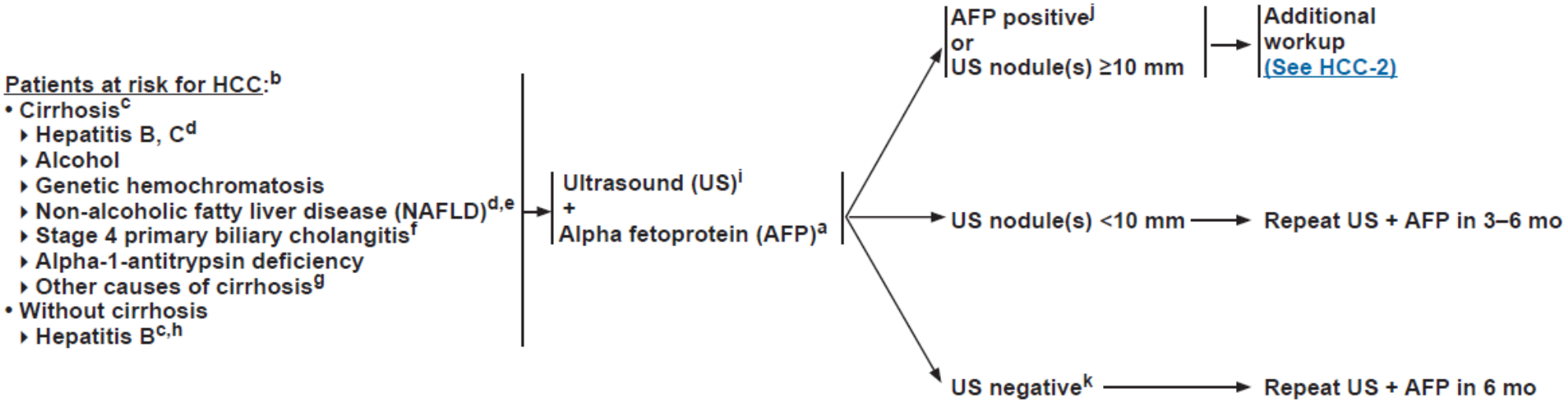
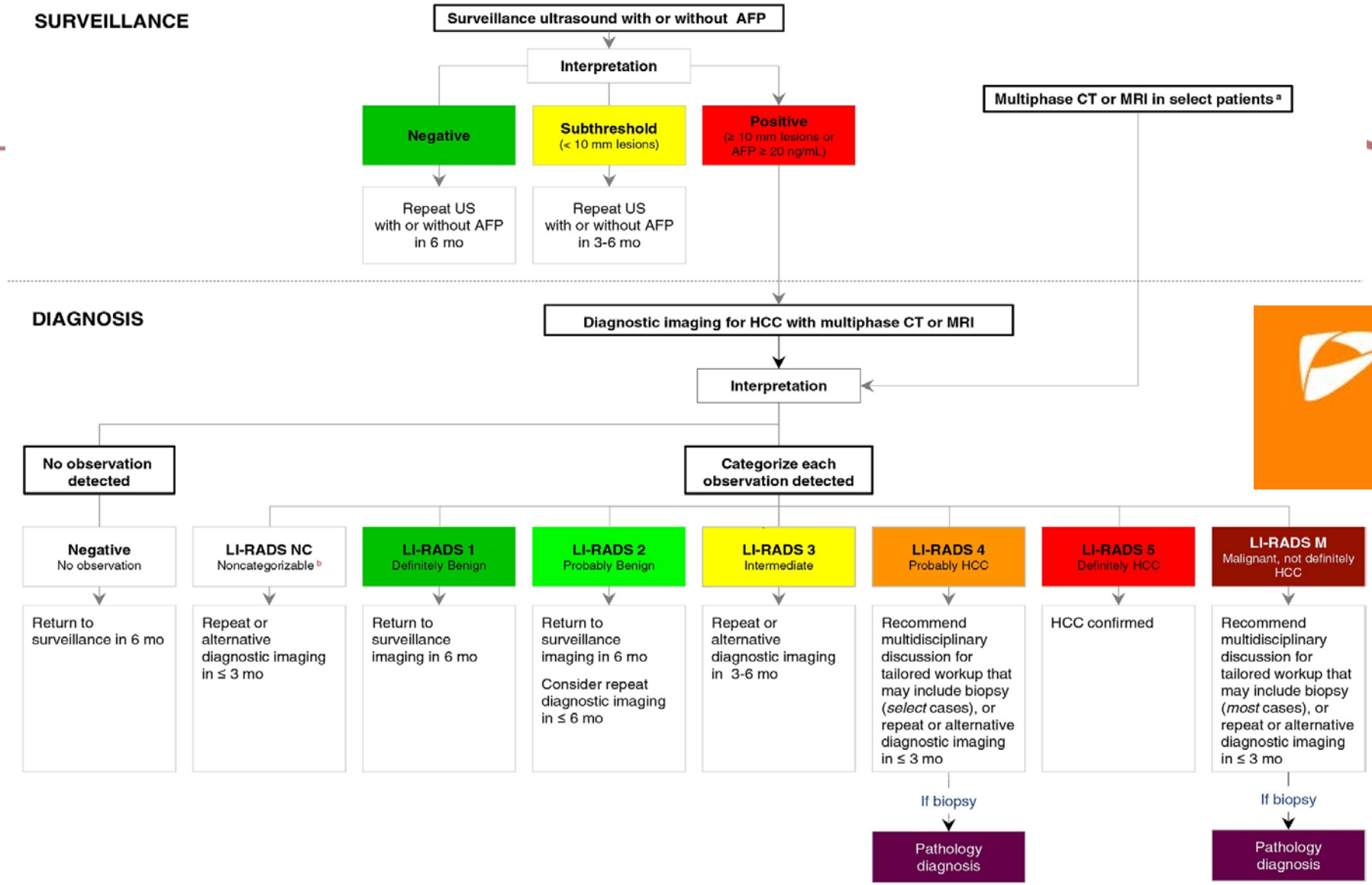
HEPATOCELLULAR CARCINOMA (HCC) SCREENING[a]





Footnotes

a. Multiphase CT or MRI in select patients	Some high-risk patients may undergo multiphase CT or MRI for HCC surveillance (depending on patient body habitus, visibility of liver at ultrasound, being on the transplant waiting list and other factors).
b. Noncategorizable	These are due to technical problem such as image omission or severe degradation

Biopsy? Is it necessary?

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PRINCIPLES OF BIOPSY

Indicators for consideration of biopsy, which may include:

- **Initial biopsy**
  - **Lesion is highly suspicious for malignancy at multiphasic CT or MRI but does not meet imaging criteria[a] for HCC.**
  - **Lesion meets imaging criteria[1] for HCC but:**
    - **Patient is not considered at high risk for HCC development (ie, does not have cirrhosis, CHB, or current or prior HCC).**
    - **Patient has cardiac cirrhosis, congential hepatic fibrosis, or cirrhosis due to a vascular disorder such as Budd-Chiari syndrome, hereditary hemorrhagic telangiectasia, or nodular regenerative hyperplasia.[b]**
    - **Patient has elevated CA 19-9 or carcinoembryonic antigen (CEA) with suspicion of intrahepatic cholangiocarcinoma or cHCC-CCA.**
  - **Confirmation of metastatic disease could change clinical decision-making including enrollment in clinical trials.**
  - **Surgical resection without biopsy should be considered with multidisciplinary review.**

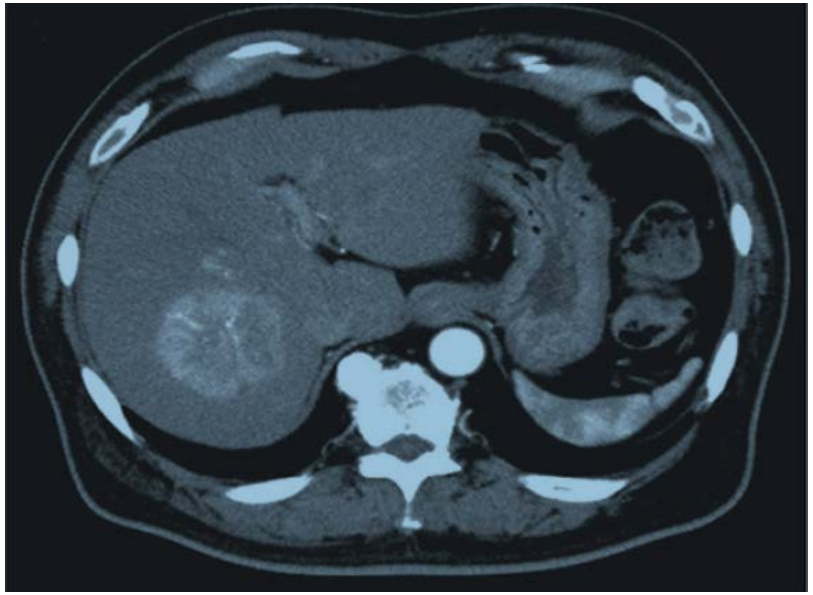
- **Repeat biopsy**
  - **Non-diagnostic biopsy**
  - **Prior biopsy discordant with imaging, biomarkers, or other factors**

Imaging for HCC

The pathognomonic radiographic profile is enhancement in the arterial phase followed by washout in the delayed venous phase. Additional common findings are delayed enhancement of the fibrous pseudocapsule, presence of septations, and an internal mosaic pattern.

Computed tomography

- sensitivity and specificity as high as 93% and 97%
- Mostly for lesions > 1cm



Magnetic resonance imaging

- MRI is becoming the predominant imaging modality for characterizing liver tumors
- MRI has the highest sensitivity and specificity for detection of 1- to 2-cm HCC, of 90% and 82%, respectively
- MRI better sensitivity (91% vs 81%) and specificity (95% vs 93%), especially for smaller HCC lesions
- MRI needs less contrast volume than CT, and injection time is shorter.

Work-up

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CLINICAL PRESENTATION	WORKUP
HCC confirmed →	Multidisciplinary evaluation[q] (assess liver reserve[r] and comorbidity) and staging: • H&P • Hepatitis panel[s] • Bilirubin, transaminases, alkaline phosphatase • PT or INR, albumin, BUN, creatinine • CBC, platelets • AFP • Chest CT[a] • Bone scan if clinically indicated[a] • Abdominal/pelvic CT or MRI with contrast, if not previously done or needs updating[a] • Consider referral to a hepatologist

Staging systems

- Liver Cancer Study Group of Japan staging system
- Japanese Integrated Staging score
- Chinese University Prognostic Index
- Okuda system
- Cancer of the Liver Italian Program (CLIP) scoring system
- Barcelona Clinic Liver Cancer (BCLC) staging system
- American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) TNM staging system

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Hepatobiliary Cancers

American Joint Committee on Cancer (AJCC)
TNM Staging for Hepatocellular Cancer (8th ed., 2017)

Table 1. **Definitions for T, N, M**

T	Primary Tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Solitary tumor ≤2 cm, or >2 cm without vascular invasion
T1a	Solitary tumor ≤2 cm
T1b	Solitary tumor >2 cm without vascular invasion
T2	Solitary tumor >2 cm with vascular invasion, or multiple tumors, none >5 cm
T3	Multiple tumors, at least one of which is >5 cm
T4	Single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic vein, or tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum

N	Regional Lymph Nodes
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

M	Distant Metastasis
M0	No distant metastasis
M1	Distant metastasis

Table 2. **AJCC Prognostic Groups**

	T	N	M
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T4	N0	M0
Stage IVA	Any T	N1	M0
Stage IVB	Any T	Any N	M1

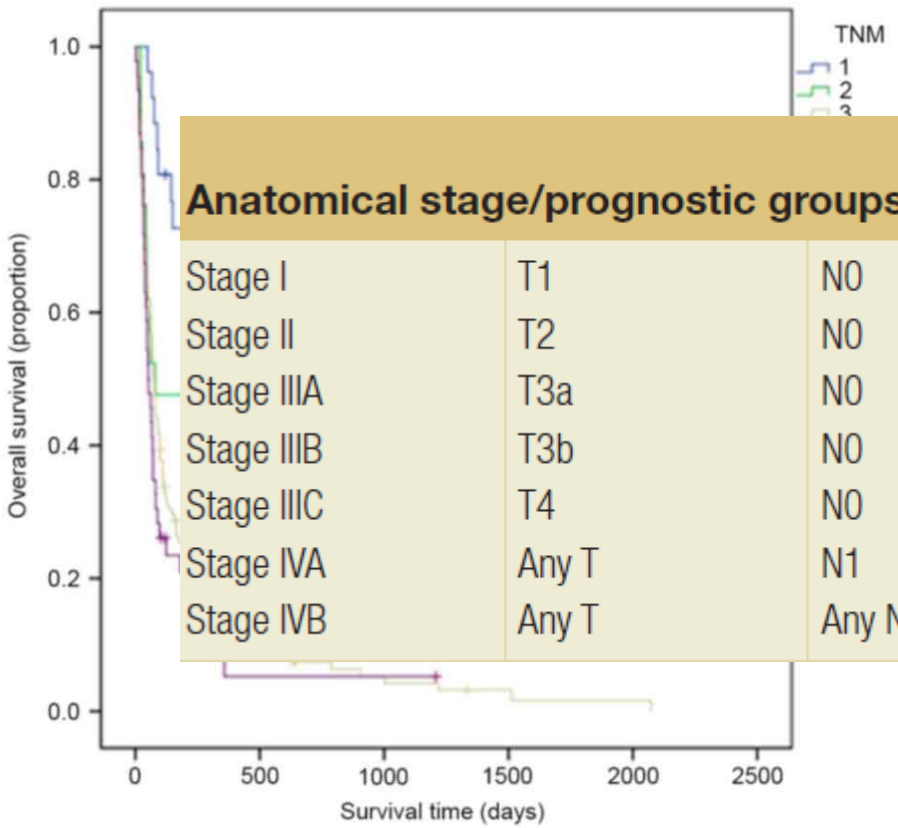
Histologic Grade (G)

GX	Grade cannot be accessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

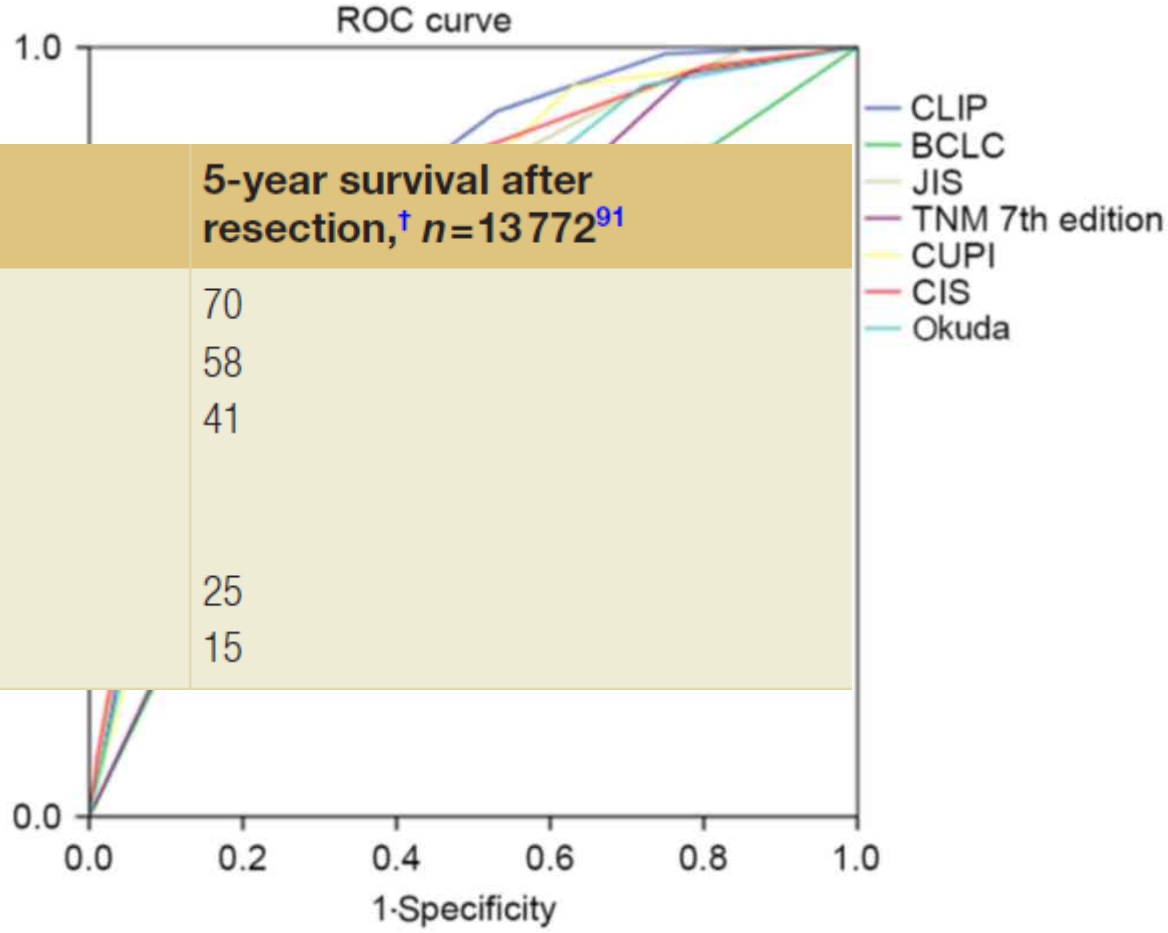
Fibrosis Score (F)

The fibrosis score as defined by Ishak is recommended because of its prognostic value in overall survival. This scoring system uses a 0-6 scale.

F0	Fibrosis score 0-4 (none to moderate fibrosis)
F1	Fibrosis score 5-6 (severe fibrosis or cirrhosis)



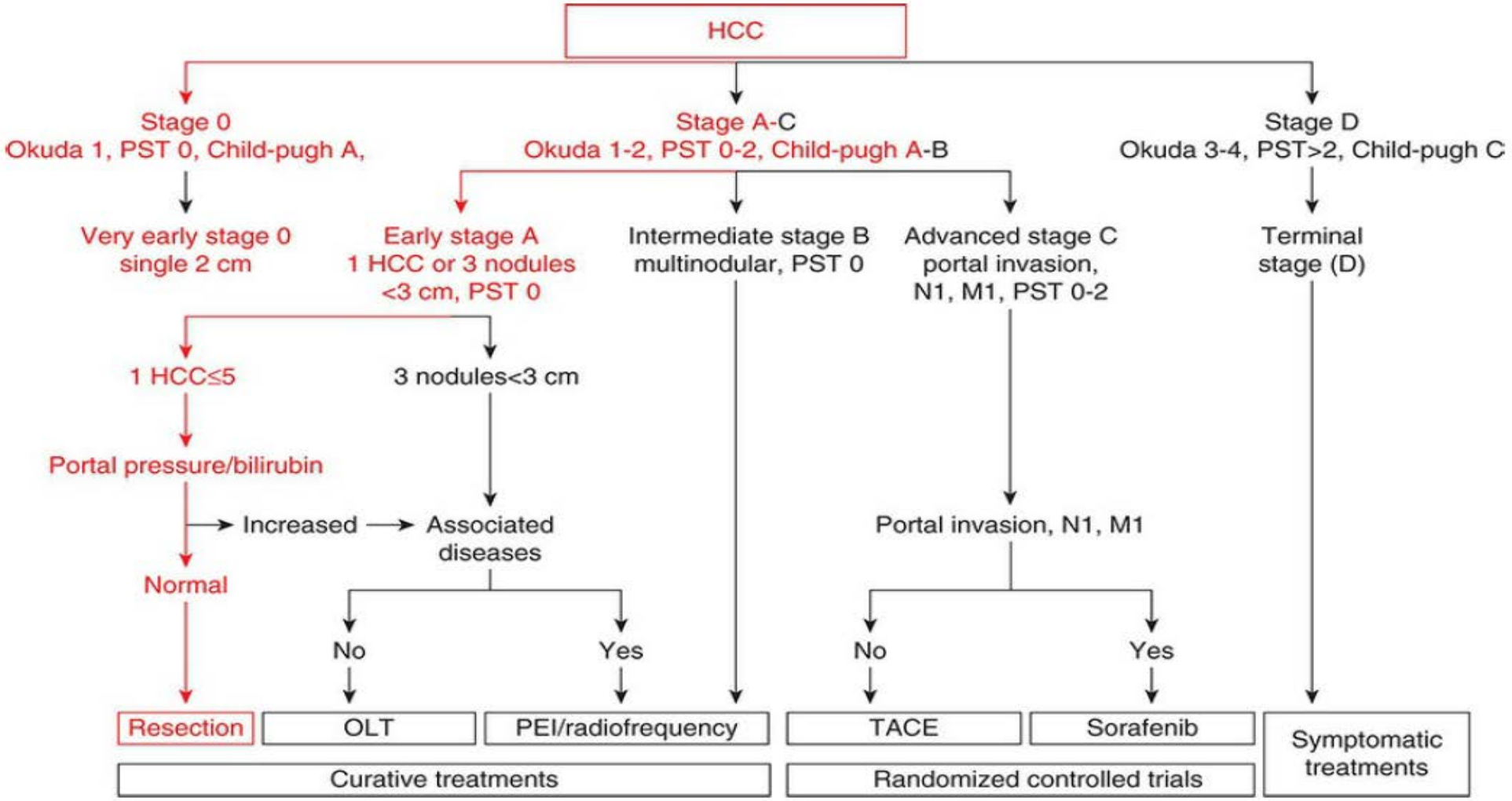
Anatomical stage/prognostic groups				5-year survival after resection,† *n*=13772[91]
Stage I	T1	N0	M0	70
Stage II	T2	N0	M0	58
Stage IIIA	T3a	N0	M0	41
Stage IIIB	T3b	N0	M0	
Stage IIIC	T4	N0	M0	
Stage IVA	Any T	N1	M0	25
Stage IVB	Any T	Any N	M1	15



Number at risk

TNM = 1	26	11	6	2	1
TNM = 2	21	5	1	1	0
TNM = 3	127	13	5	2	1
TNM = 4	46	1	1	0	0

Barcelona Clinic Liver Cancer (BCLC) staging system



Hepatic functional reserve, the most important predictor of mortality risk, is determined by using the CTP score

CHILD-PUGH SCORE

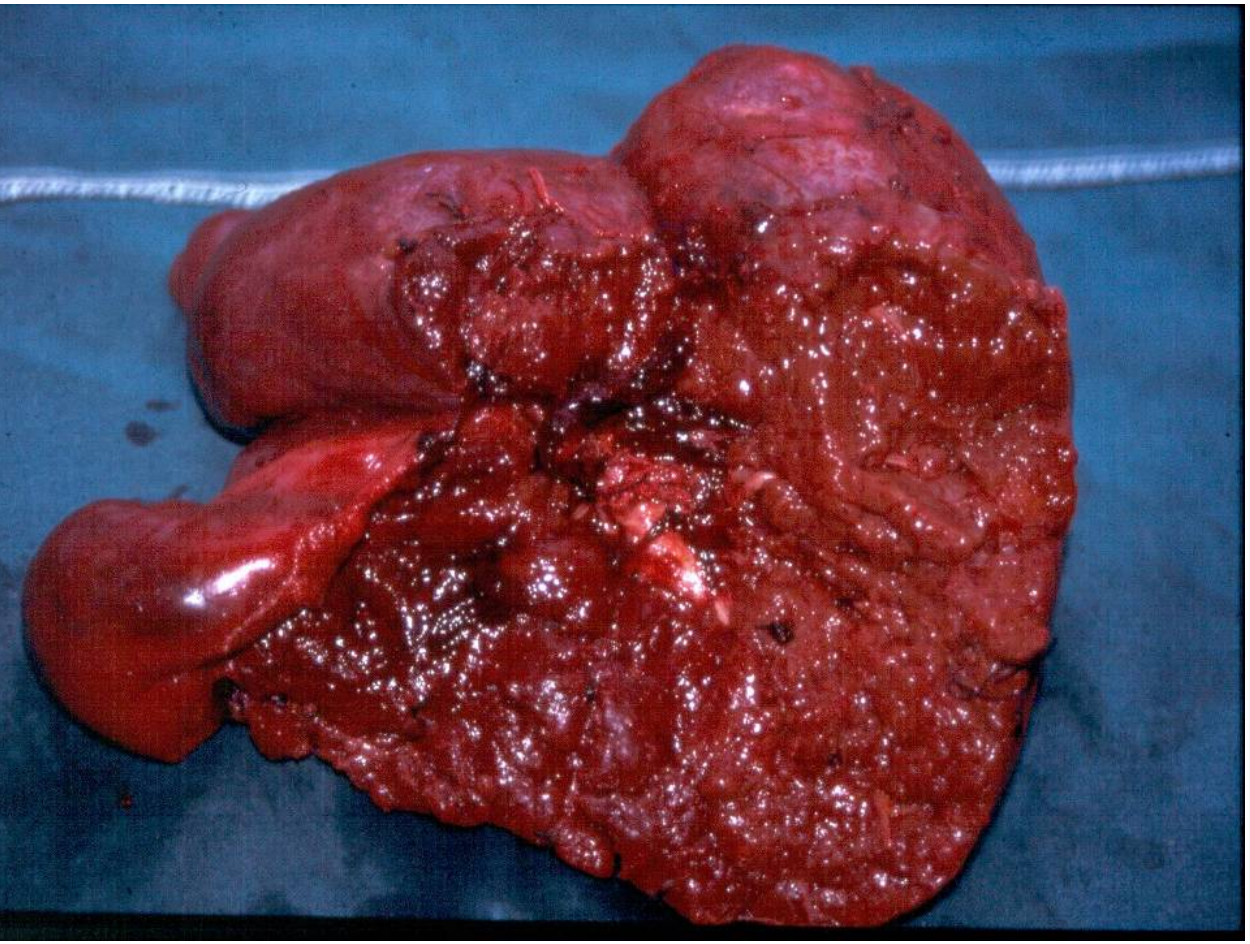
Chemical and Biochemical Parameters	Scores (Points) for Increasing Abnormality		
	1	2	3
Encephalopathy (grade)[1]	None	1–2	3–4
Ascites	Absent	Slight	Moderate
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time[2] Seconds over control INR	 <4 <1.7	 4–6 1.7–2.3	 >6 >2.3
Bilirubin (mg/dL) • For primary biliary cirrhosis	<2 <4	2–3 4–10	>3 >10

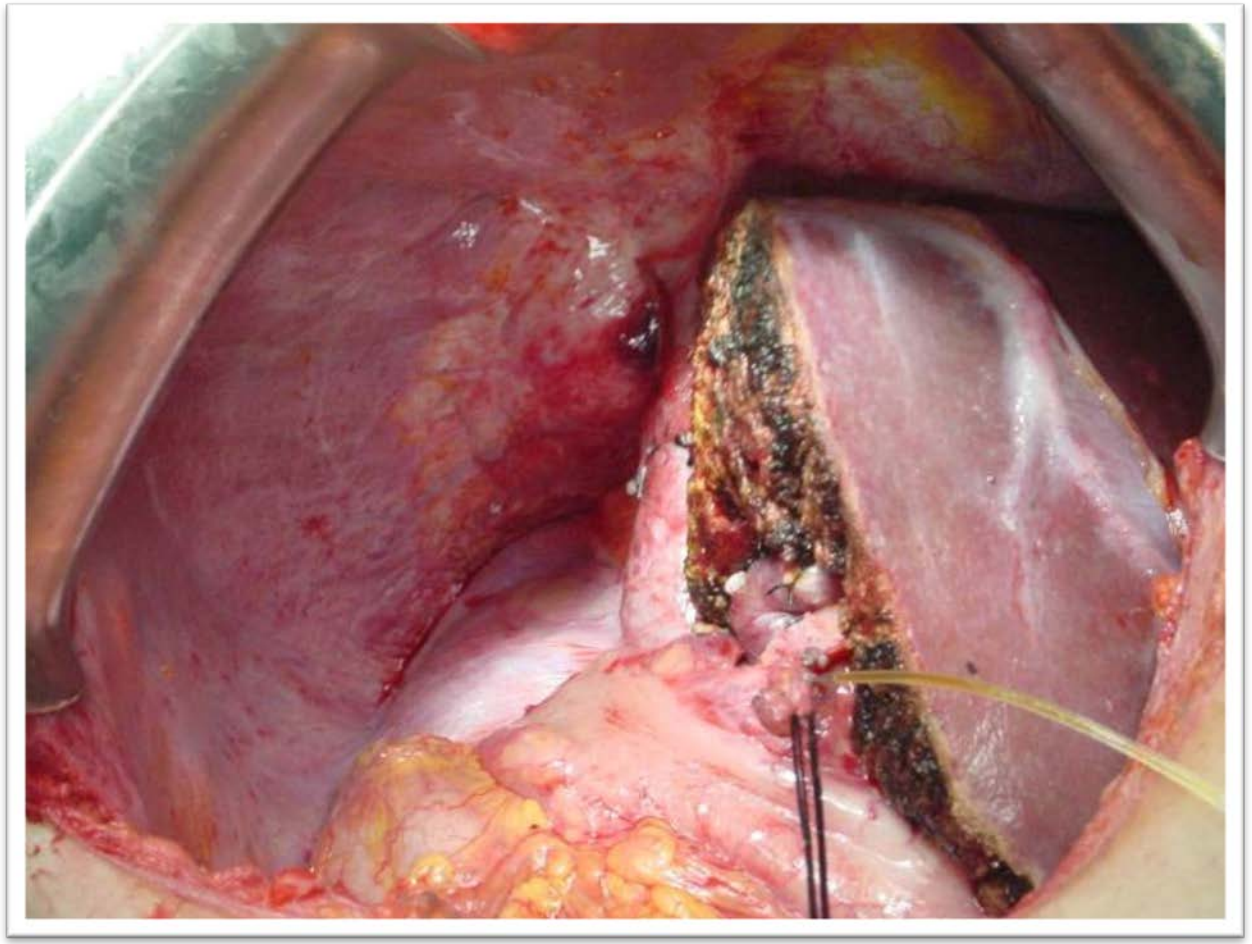
Class A = 5–6 points; Class B = 7–9 points; Class C = 10–15 points.

Class A: Good operative risk
Class B: Moderate operative risk
Class C: Poor operative risk

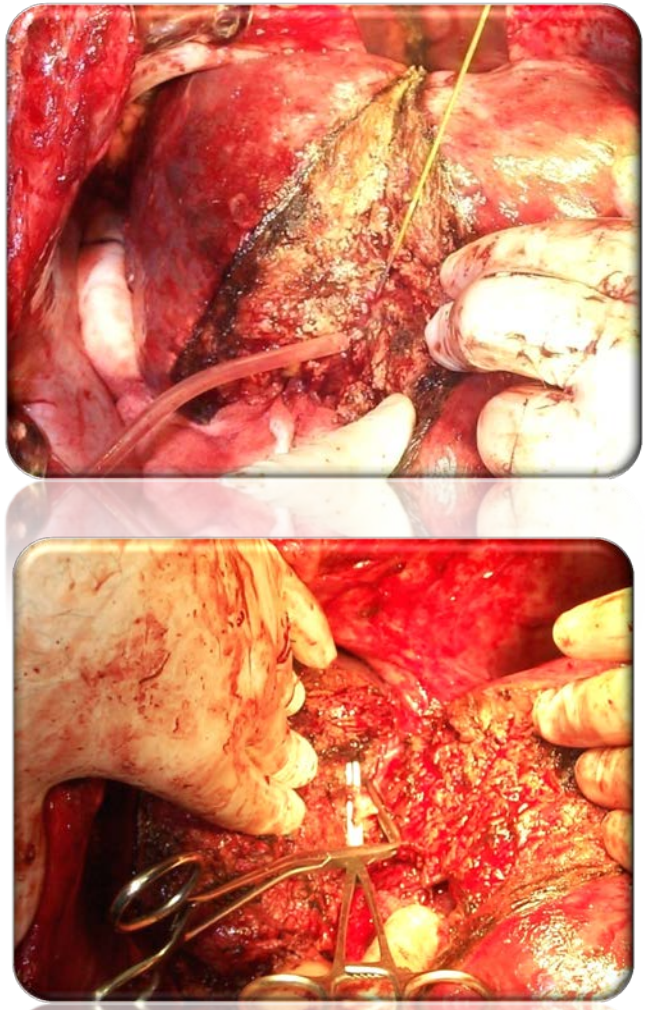
perioperative mortality
CTP class A 10%
B 30%
C 82%

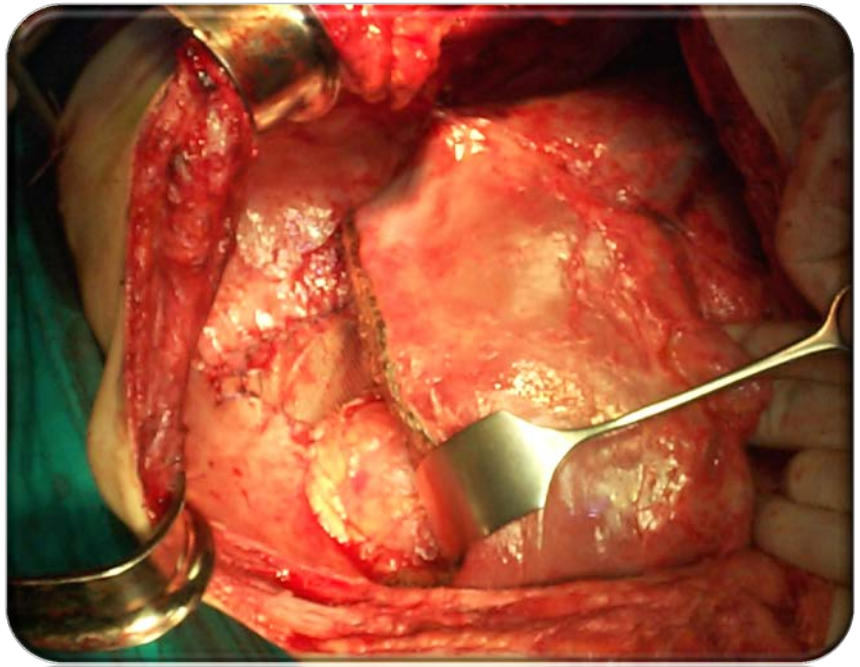
Resection?

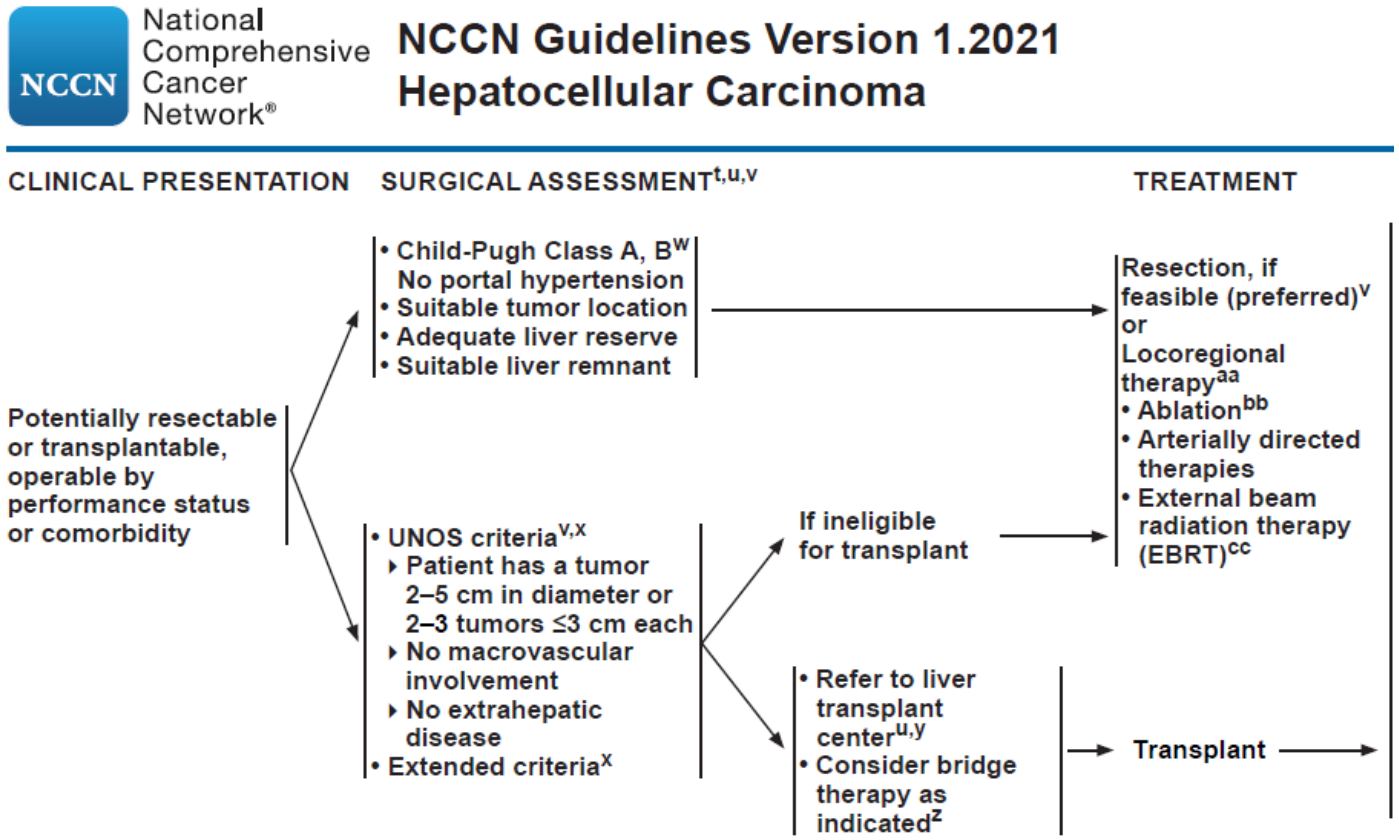




The sequential continuous coagulate-cut technique
- minimal blood-loss liver transection -



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Hepatocellular Carcinoma
CLINICAL PRESENTATION
SURGICAL ASSESSMENT[t,u,v]
TREATMENT
Potentially resectable or transplantable, operable by performance status or comorbidity
• Child-Pugh Class A, B[w]
No portal hypertension
• Suitable tumor location
• Adequate liver reserve
• Suitable liver remnant
Resection, if feasible (preferred)[v] or
Locoregional therapy[aa]
• Ablation[bb]
• Arterially directed therapies
• External beam radiation therapy (EBRT)[cc]
• UNOS criteria[v,x]
▸ Patient has a tumor 2–5 cm in diameter or 2–3 tumors ≤3 cm each
▸ No macrovascular involvement
▸ No extrahepatic disease
• Extended criteria[x]
If ineligible for transplant
• Refer to liver transplant center[u,y]
• Consider bridge therapy as indicated[z]
Transplant

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PRINCIPLES OF SURGERY

- Patients must be medically fit for a major operation.
- Hepatic resection is indicated as a potentially curative option in the following circumstances:
  - Adequate liver function (generally Child-Pugh Class A without portal hypertension, but small series show feasibility of limited resections in patients with mild portal hypertension)[1]
  - Solitary mass without major vascular invasion
  - Adequate future liver remnant (FLR) (at least 20% without cirrhosis and at least 30%–40% with Child-Pugh Class A cirrhosis, adequate vascular and biliary inflow/outflow)
- Hepatic resection is controversial in the following circumstances, but can be considered:
  - Limited and resectable multifocal disease
  - Major vascular invasion
- For patients with chronic liver disease being considered for major resection, preoperative portal vein embolization should be considered.[2]
- Patients meeting the United Network for Organ Sharing (UNOS) criteria ([single lesion ≥2 cm and ≤5 cm, or 2 or 3 lesions ≥1 cm and ≤3 cm] www.unos.org) should be considered for transplantation (cadaveric or living donation).

Κακοήθη νεοπλάσματα του ήπατος
Θεραπευτικές επιλογές

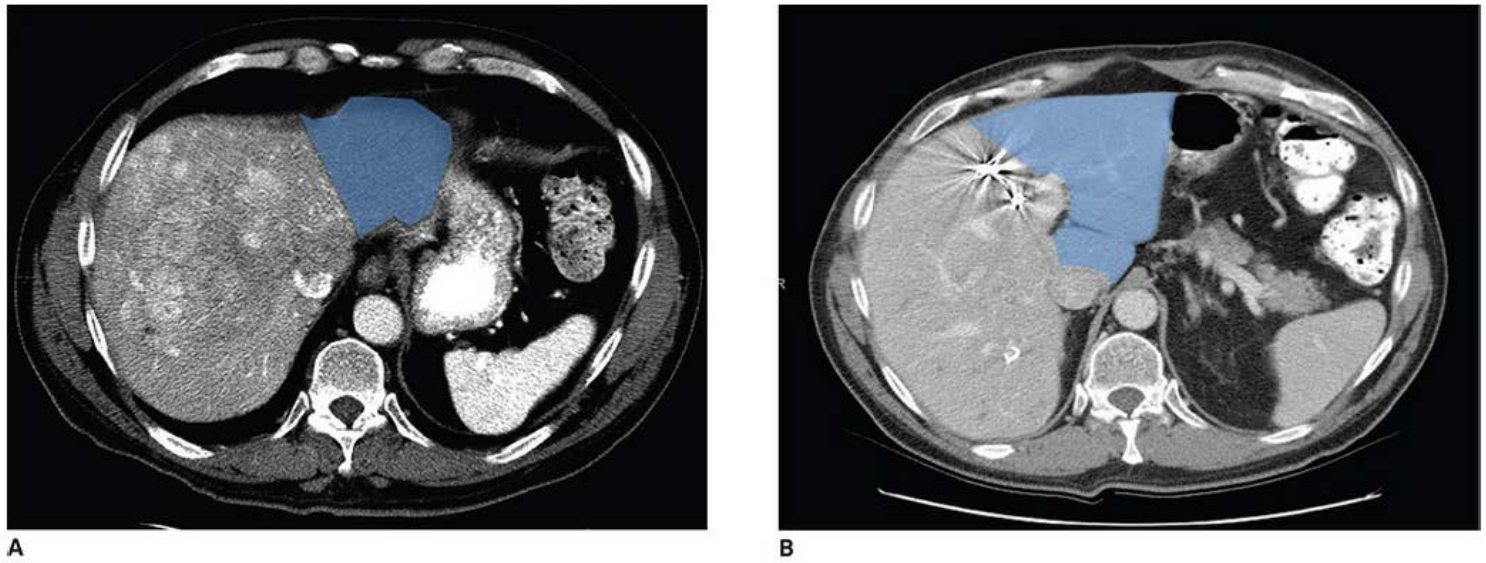
Χειρουργικές επιλογές

- Resection
  - Ηπατεκτομή (μερική)
  - Μεταμόσχευση ήπατος (ολική ηπατεκτομή)
- Radiofrequency Ablation (RFA)
- Resection with RFA
- Microwave Ablation (MA)
- Cryosurgery

Συντηρητικές επιλογές

- Selective Internal Radiation Therapy (SIRT)
- Hepatic artery infusion (port or pump) (HAI)
- Chemoembolization
- Alcohol ablation (PEI)
- Chemotherapy
- Radiation

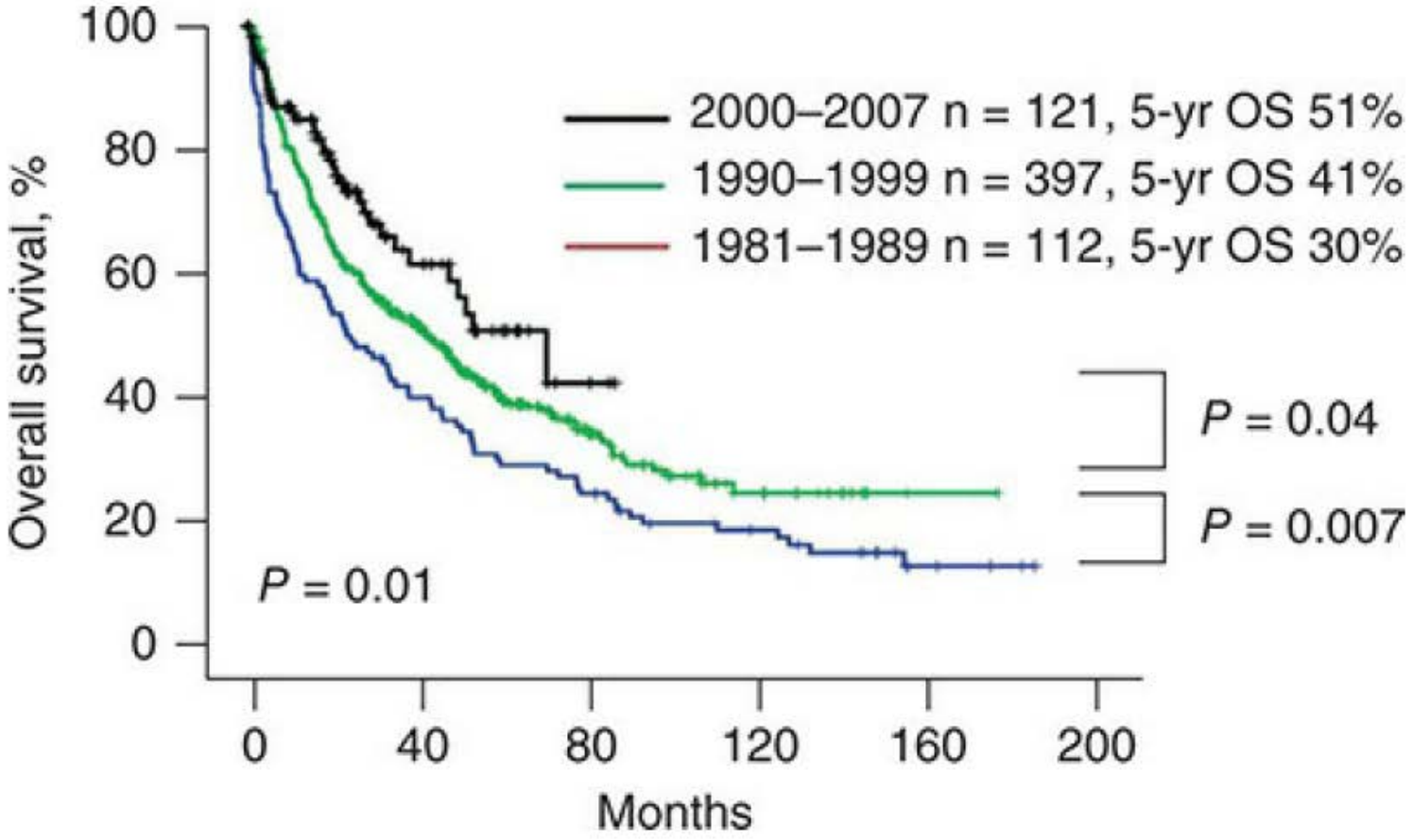
FUTURE LIVER REMNANT (FLR)



Right portal vein embolization (PVE) and segment IV embolization for a large hepatocellular carcinoma

Indications for PVE	Contraindications for PVE
To increase the safety of major resection	Vascular invasion or thrombosis of portal vein
FLR <20% in absence of underlying liver disease	Tumor extension to FLR
FLR <40% if underlying liver disease	Uncorrectable coagulopathy
In combination with transarterial chemoembolization	Renal failure
Segment IV embolization for extended right hepatectomy	Portal hypertension

Improvement in overall survival (OS) after major hepatectomy (resection of >3 liver segments) for hepatocellular carcinoma over time (n = 630)



Outcomes of resection

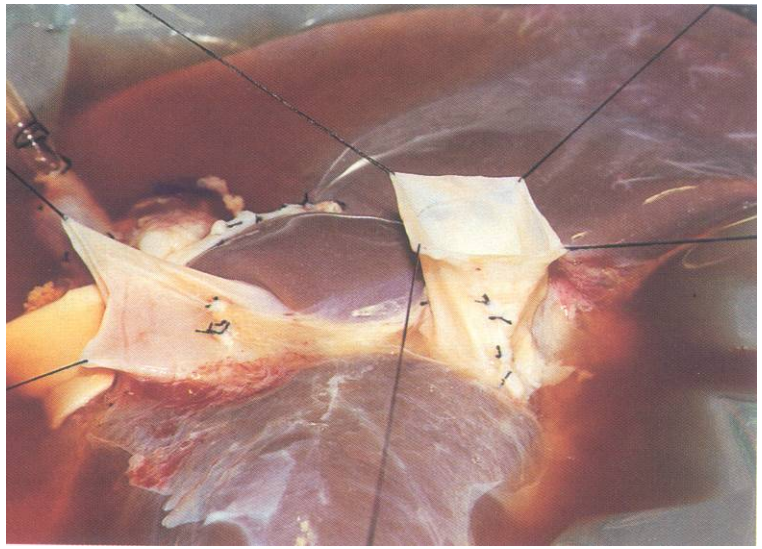
- Only 10-15% candidates for resection
- Ineffective systemic chemotherapy (sorafenib?)
- Recurrence occurring in 50% and 80% of patients within 5 years
- the more common is a second primary lesion
- 5-year survival rates after resection range from 30% to 60%

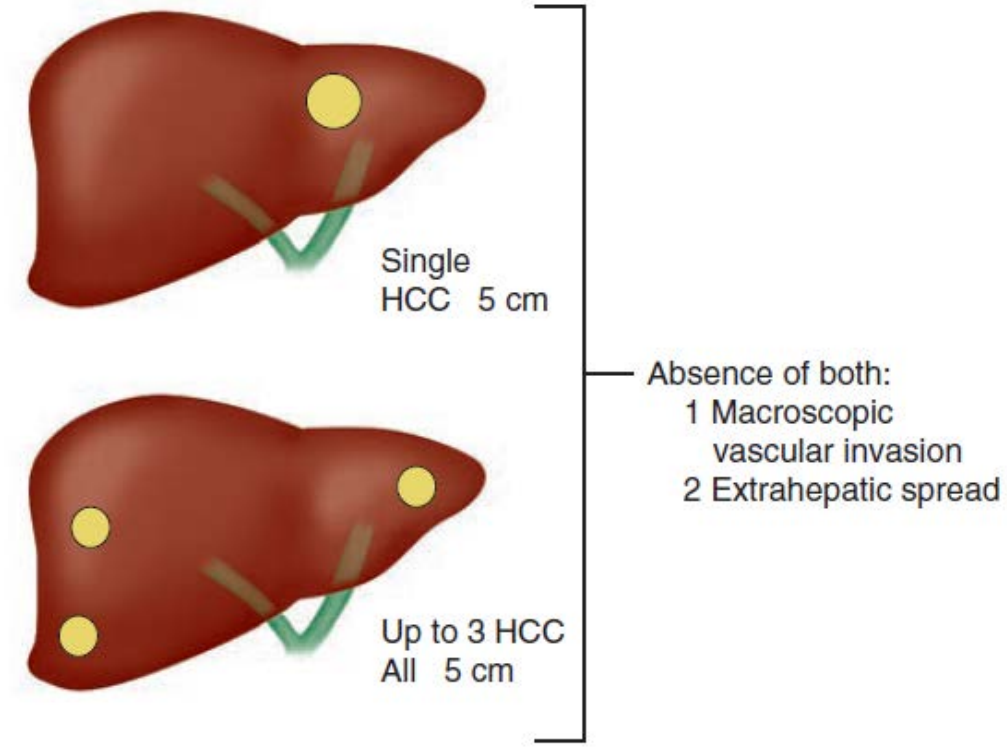
Prognostic factors

- Cirrhosis (recurrence)
- invasion of major vessels
- microvascular invasion
- and both the number of tumors and tumor size (not for solitary lesions)

Transplantation

- Milan criteria





4-year survival rate of 74%, similar to that for patients who received a liver transplant but did not have HCC.

Transplantation

- *University of California San Francisco (UCSF) criteria*

✓ single tumor less than 6.5 cm or fewer than three tumors,

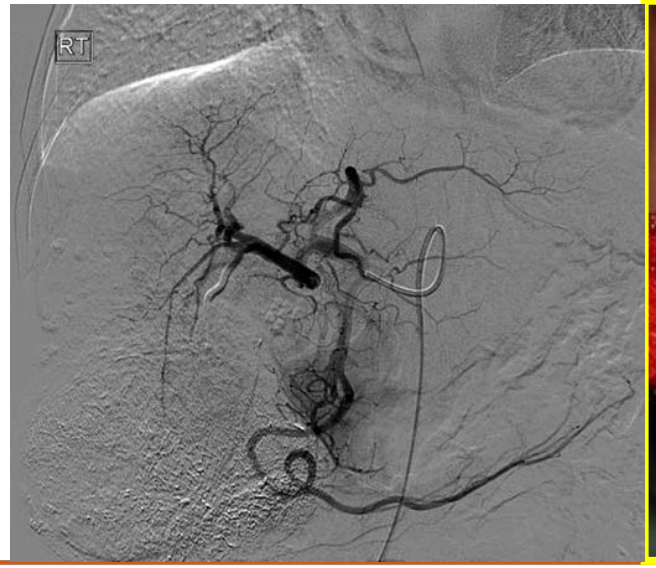
✓ the total diameter of all being less than 8 cm and the

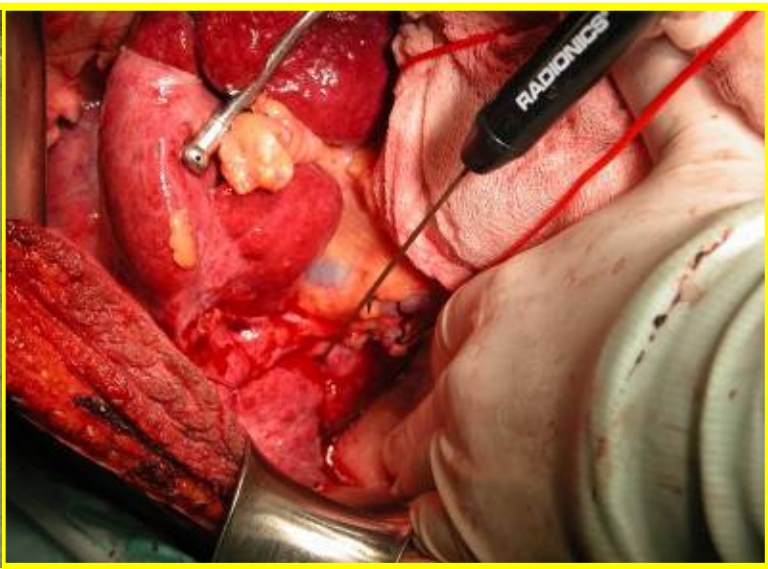
✓ largest tumor less than 4.5 cm

controversial because 5-year overall survival rates of patients who met these criteria and underwent transplant ranged from 38% to 93%.

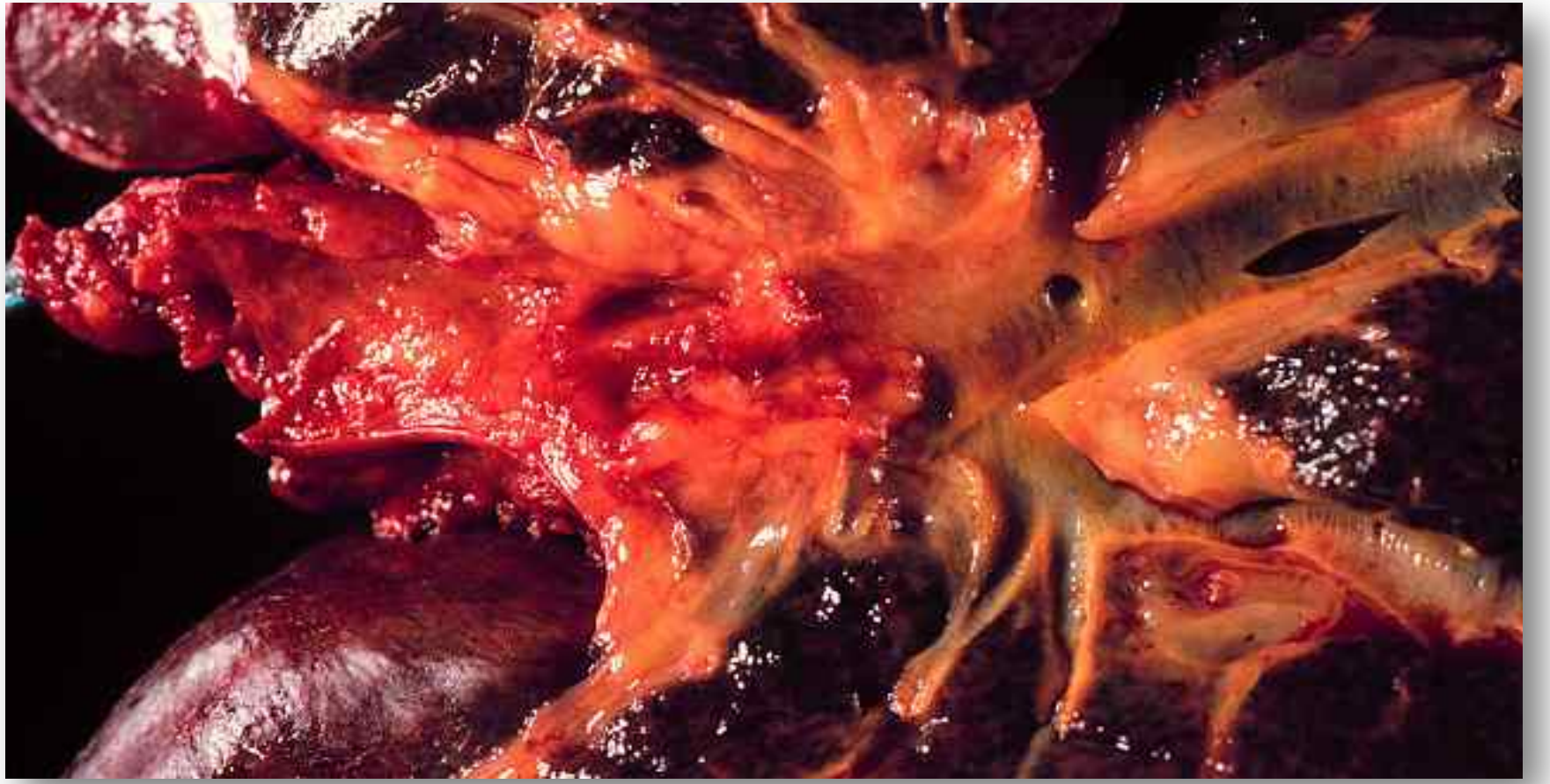
Local ablative therapies

- Radiofrequency Ablation (high-frequency alternating current heat up to 120°C, resulting in denaturing of proteins and coagulative necrosis). Better for <3cm. Equivalent to resection!!!!
- Percutaneous Ethanol Injection (achieves complete necrosis of tumors smaller than 3 cm, and 50% necrosis in 3- to 5-cm tumors)
- Transcatheter Arterial Chemoembolization (survival rates in use of TACE in unresectable HCC at 1, 2, and 3 years at 96%, 77%, and 47%, respectively)
- Microwave ablation (1- and 5-year survival rates of 93% and 51%, respectively)





Cholangiocarcinoma



Epidemiology and risk factors

- Incidence in the United States has been estimated at 1 to 2 per 100,000
- more common among Native Americans and Japanese Americans
- Most patients are diagnosed after the age of 65

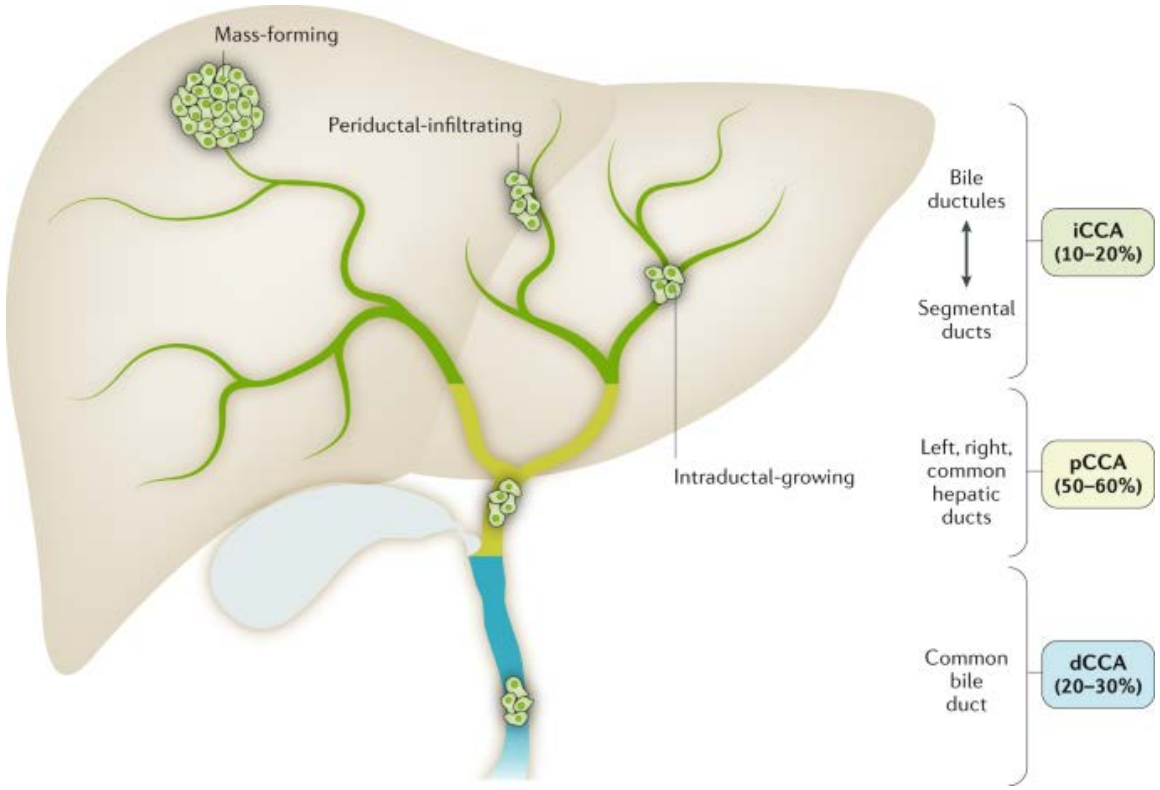


TABLE 65-3: RISK FACTORS FOR BILE DUCT CANCER

Primary sclerosing cholangitis
Liver flukes infestation (*Opisthorchis viverrini* and *Clonorchis sinensis*)
Choledochal cysts
Caroli disease
Hepatolithiasis
Chemicals (eg, Thorotrast and dioxin)
Hepatitis C
Lynch syndrome II
Bile duct adenoma and multiple biliary papillomatosis

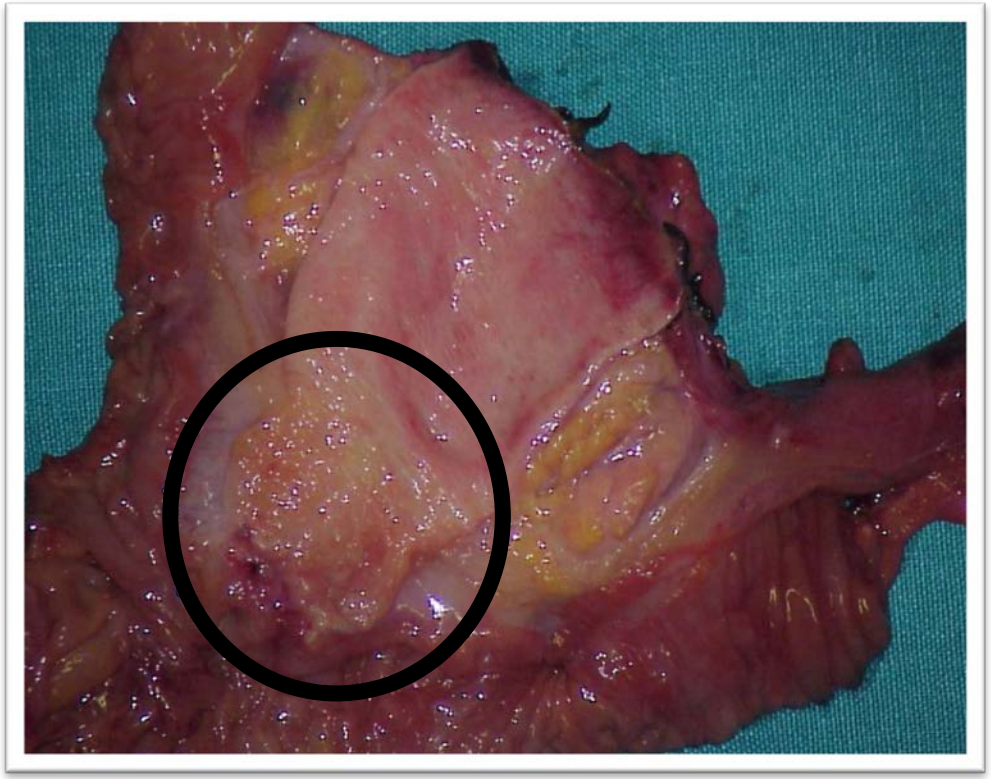
Pathology

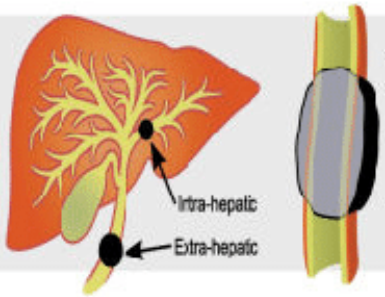
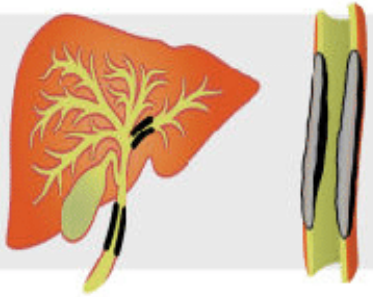
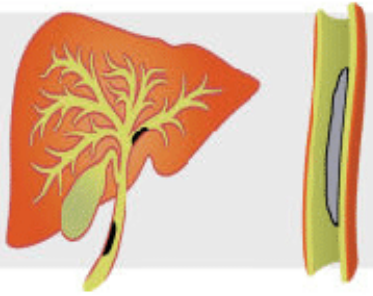
- Most ICC poorly differentiated adenocarcinoma
- Extrahepatic hilar and distal cholangiocarcinomas are categorized into three macroscopic subtypes:

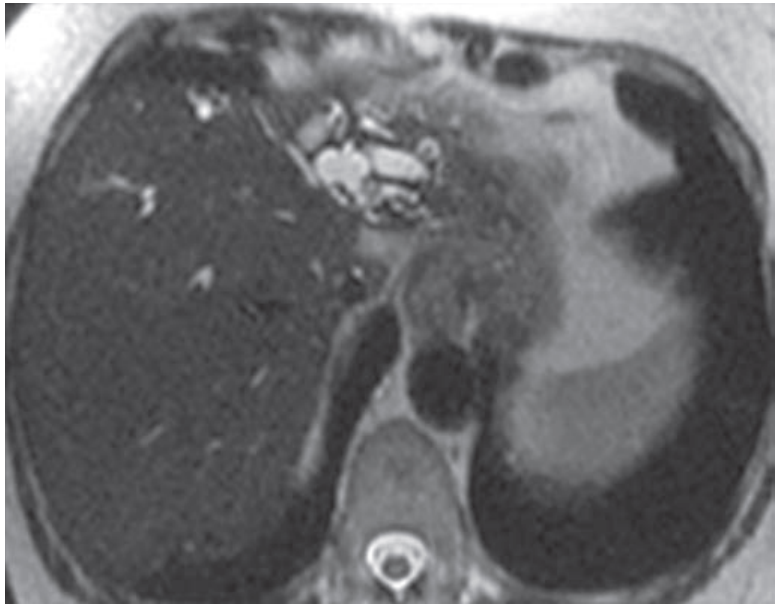
✓sclerosing 70%,

✓nodular (20%

✓and papillary (5% to 10%)

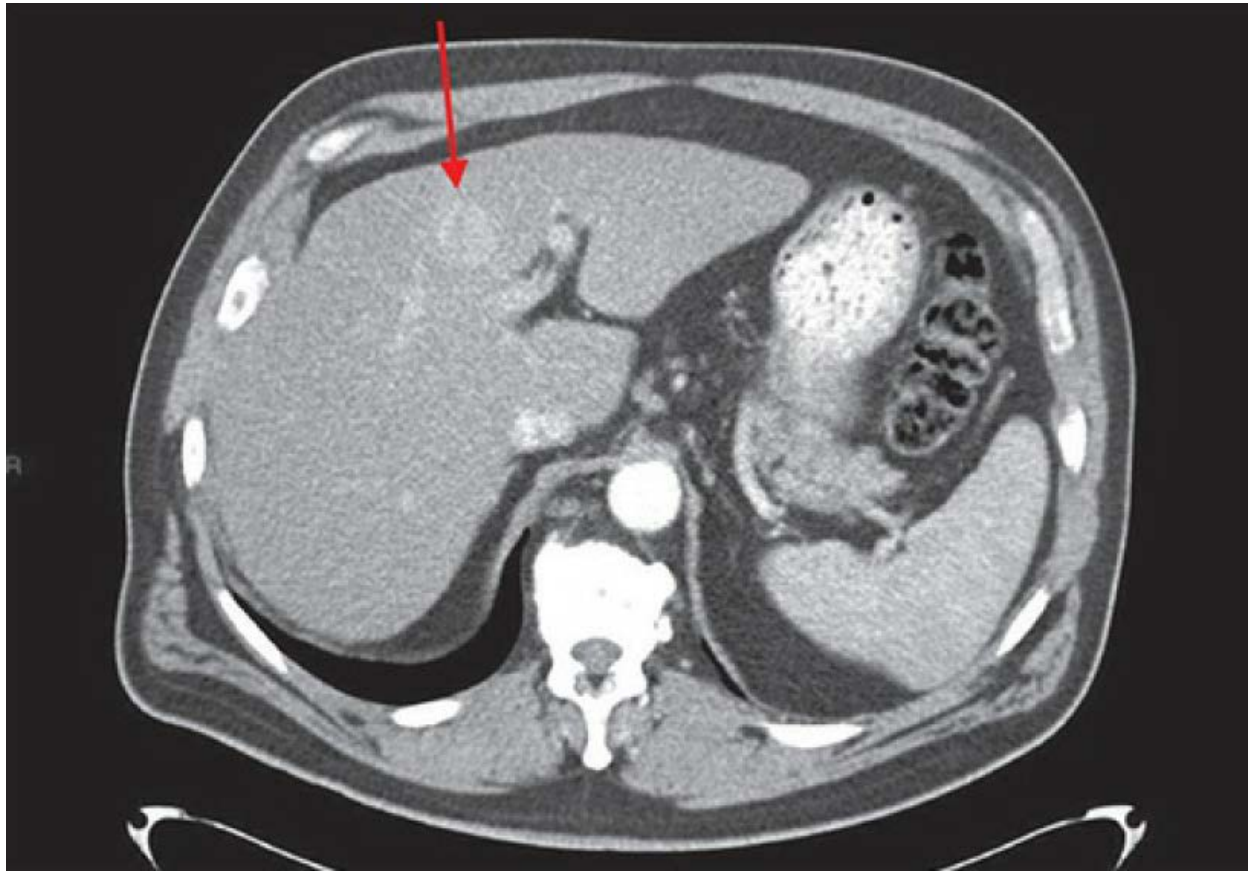


CCA Subtype	Dimensions	Location (Intra or Extra-hepatic)	Pathology	Method of Spread	Symptoms of Bile Duct Obstruction?
Mass forming	Central mass; depends on location (IH up to 15 cm; EH 1–2 cm)		• Gray white mass • Poor cellular differentiation • Well defined, wavy, or lobulated borders • May have central fibrosis and necrosis	• Grows outward into lumen • Invades liver parenchyma through peribiliary venous plexus • Intrahepatic metastasis is common in advanced stages	Symptoms occasionally occur
Periductal-infiltrating	0.5–6 cm long (up to 1cm in the case of EH tumors)		• Concentric thickening of bile duct wall • Later stages appear branch-like • Usually highly differentiated	• Invades bile duct wall • Spreads along axis of bile ducts	Viscous mucus produced by the tumor can impede bile flow and produce intermittent obstructive symptoms
Intraductal growing	Usually small and flat; later stages may fill bile duct lumen		• Tumors within lumen • Frond-like foldings	• Spreads superficially along mucosal surface • Sloughing of tumor cells can initate secondary tumors • Invasive intraductal CCA can also occur	Narrowing of bile ducts eventually leads to symptoms

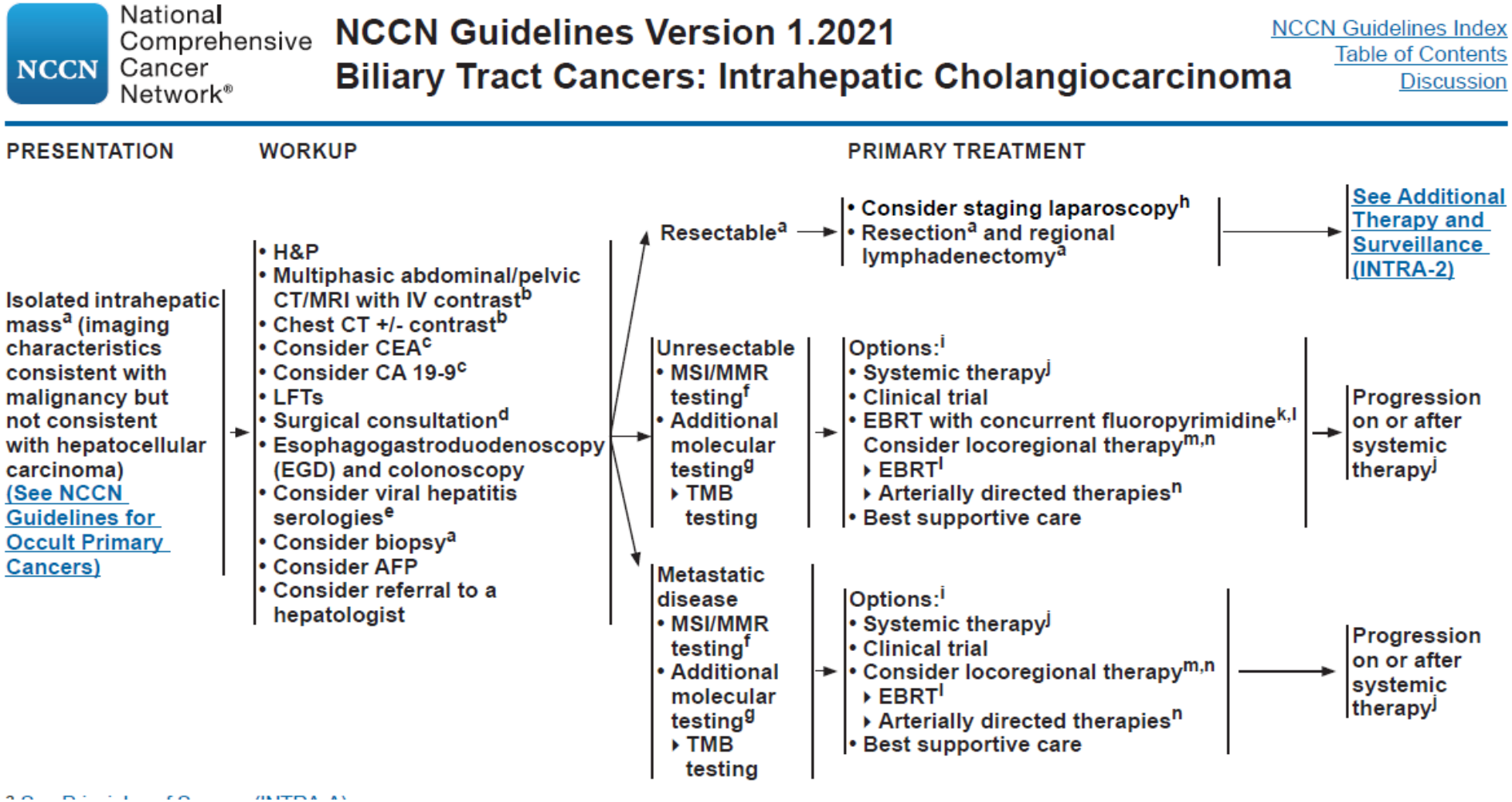


Clinical Presentation and Diagnosis

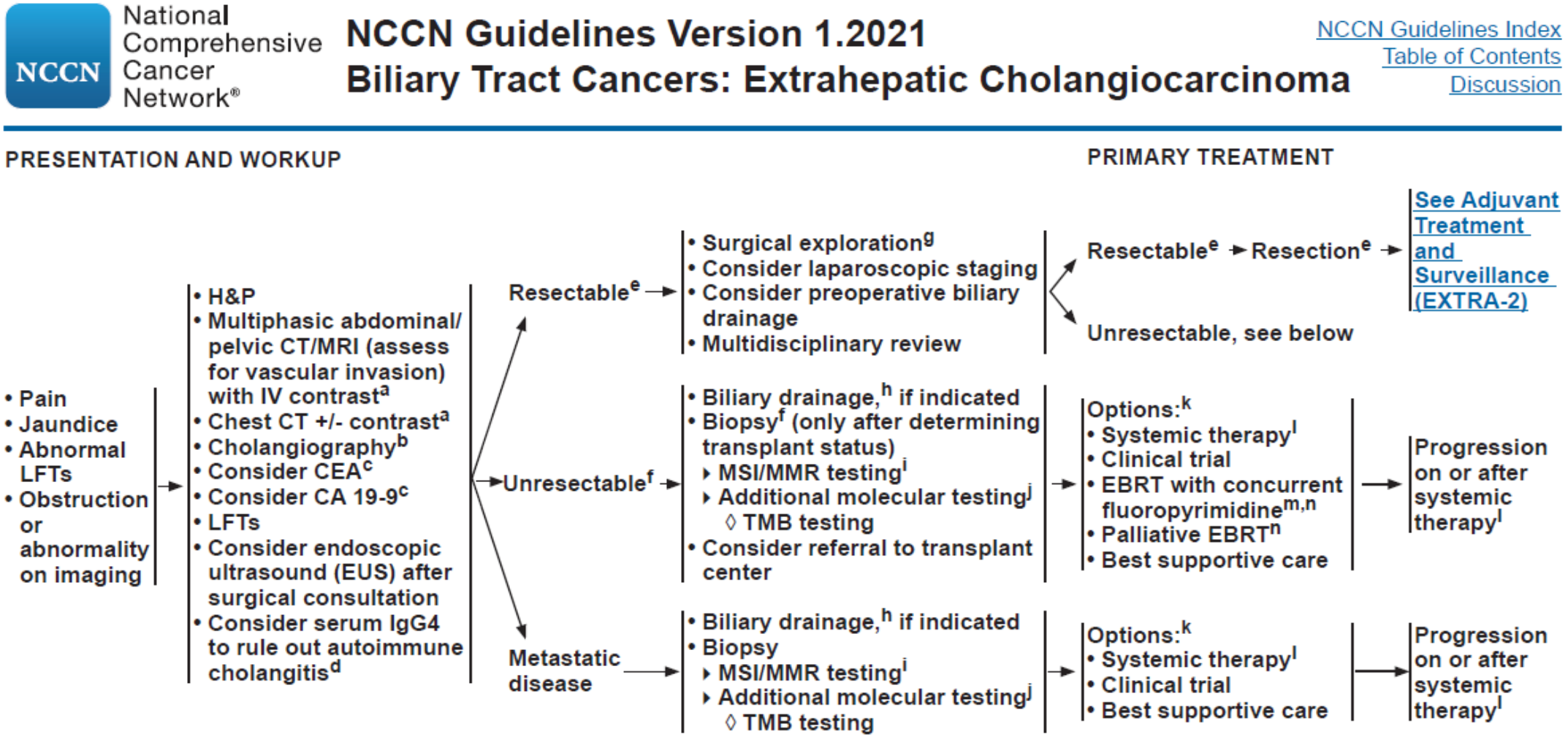
Extra-Hepatic CCA	Intra-Hepatic CCA
• Painless, jaundice 90% • Cholangitis 10% • Rare: – Paraneoplastic syndromes – Diabetes – Hypoglycemia – Hypercalcemia – Porphyria cutanea tarda – Migratory thrombophlebitis – Acantosis nigricans	• Aspecific symptoms: – Abdominal pain – Diminished appetite – Weight loss – Malaise – Night sweats • Cholestasis • Incidental mass



ICC management algorithm

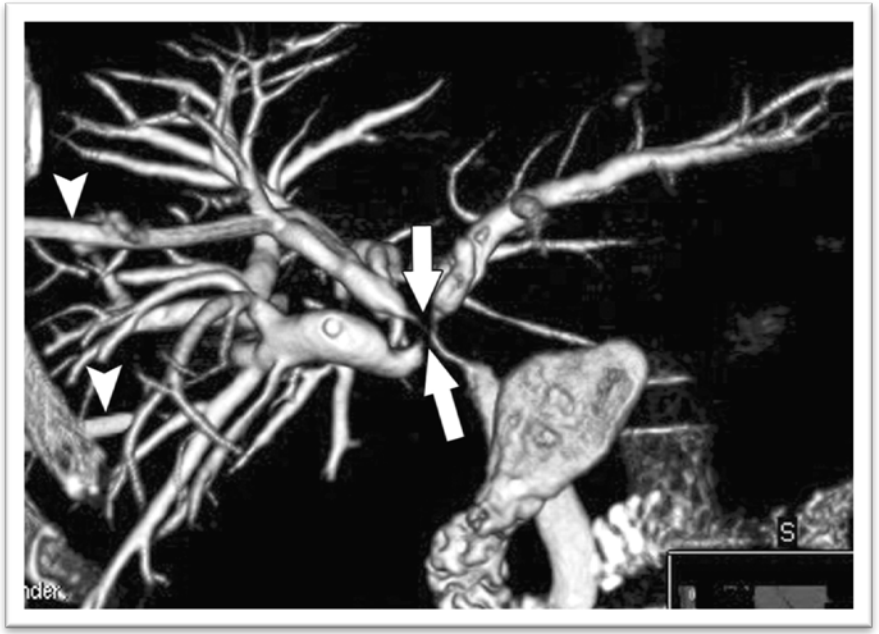


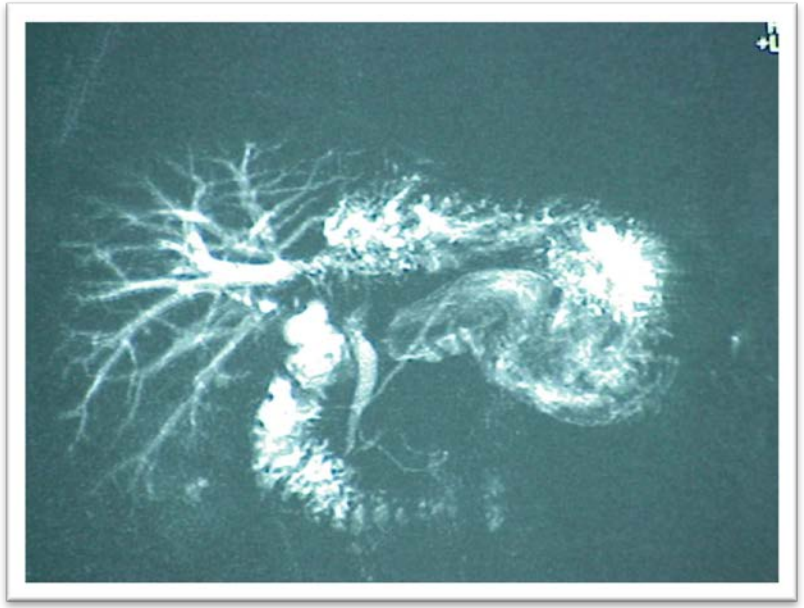
Extrahepatic CCA management algorithm



Imaging

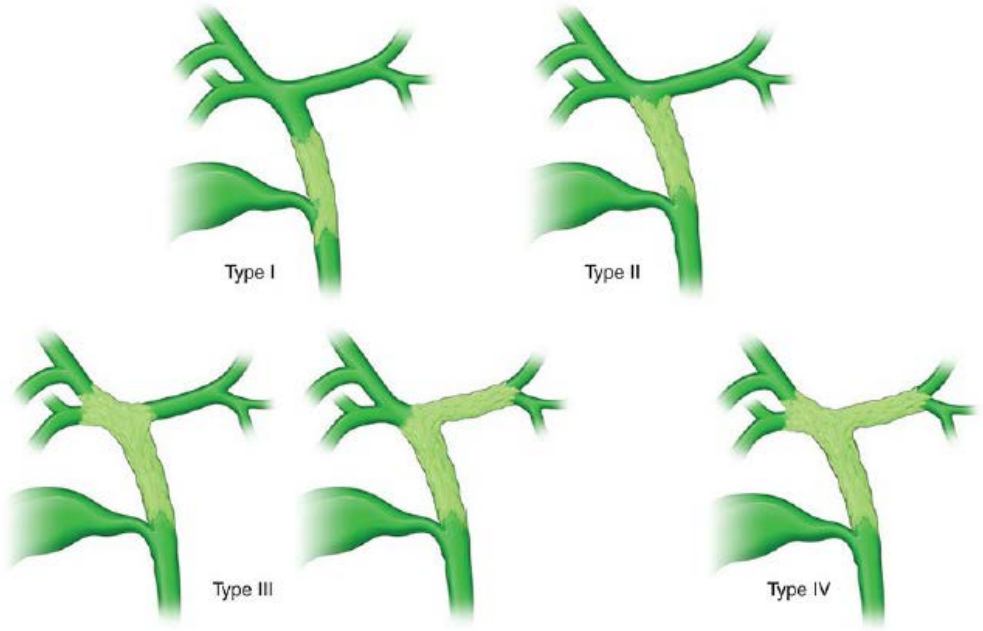
- Thin section (minimum 2.5 mm reconstructed at 1.25 mm), high-resolution CT performed with rapid intravenous contrast bolus in arterial and portovenous phases can accurately determine resectability in the majority of cases.
- MRI with MRCP can better delineate intrahepatic tumor extension and precise biliary radicle involvement but has limited vascular accuracy.
- If both modalities are used, resectability should be predicted more than 75% of the time





Staging

Bismuth-Corlette system staging system



Staging criteria for intrahepatic cholangiocarcinoma resemble those used for other primary hepatic tumors, and staging criteria for distal cholangiocarcinoma resemble those used for other periampullary carcinomas.

American Joint Committee on Cancer (AJCC)
TNM Staging for Intrahepatic Bile Duct Tumors (8th ed., 2017)

Table 5. **Definitions for T, N, M**

T	**Primary Tumor**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ* (intraductal tumor)
T1	Solitary tumor without vascular invasion, ≤5 cm or >5 cm
T1a	Solitary tumor ≤5 cm without vascular invasion
T1b	Solitary tumor >5 cm without vascular invasion
T2	Solitary tumor with intrahepatic vascular invasion or multiple tumors, with or without vascular invasion
T3	Tumor perforating the visceral peritoneum
T4	Tumor involving local extrahepatic structures by direct invasion
N	**Regional Lymph Nodes**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis present
M	**Distant Metastasis**
M0	No distant metastasis
M1	Distant metastasis present

Table 6. **AJCC Prognostic Groups**

	T	N	M
Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T4	N0	M0
	Any T	N1	M0
Stage IV	Any T	Any N	M1

Histologic Grade (G)

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated

American Joint Committee on Cancer (AJCC)
TNM Staging for Perihilar Bile Duct Tumors (8th ed., 2017)

Table 7. **Definitions for T, N, M**

T	**Primary Tumor**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*/high-grade dysplasia
T1	Tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue
T2	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue, or tumor invades adjacent hepatic parenchyma
T2a	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue
T2b	Tumor invades adjacent hepatic parenchyma
T3	Tumor invades unilateral branches of the portal vein or hepatic artery
T4	Tumor invades main portal vein or its branches bilaterally, or the common hepatic artery; or unilateral second-order biliary radicals bilaterally with contralateral portal vein or hepatic artery involvement
N	**Regional Lymph Nodes**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One to three positive lymph nodes typically involving the hilar, cystic duct, common bile duct, hepatic artery, posterior pancreatoduodenal, and portal vein lymph nodes
N2	Four or more positive lymph nodes from the sites described for N1
M	**Distant Metastasis**
M0	No distant metastasis
M1	Distant metastasis

Table 8. **AJCC Prognostic Groups**

	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a-b	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T4	N0	M0
Stage IIIC	Any T	N1	M0
Stage IVA	Any T	N2	M0
Stage IVB	Any T	Any N	M1

Histologic Grade (G)

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated

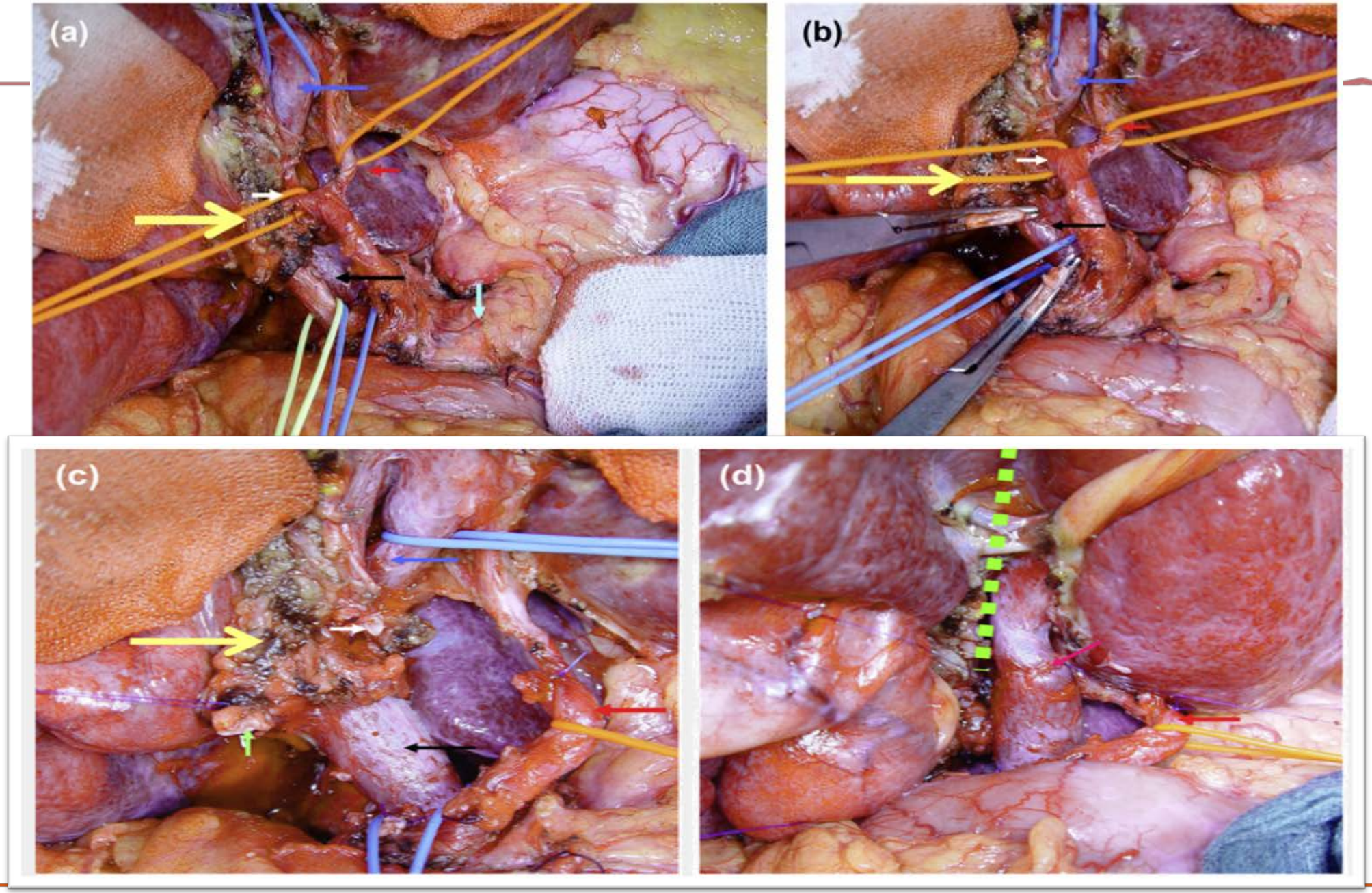
Surgery

In the absence of effective chemotherapy or radiation therapy, surgical resection remains the mainstay of curative treatment for cholangiocarcinoma. Within this context, the ability to affect a margin-negative R0 complete resection is critical.

Χολαγγειοκαρκίνωμα (CCA)

- Extrahepatic CCA
  - Perihilar
    - Bismuth type I or II without vascular invasion : local tumor excision
    - Bismuth type IIIa or IIIb : right or left hepatectomy
      - resection of the adjacent caudate lobe may be required
      - Also resect all extrahepatic biliary tree
    - + lymph node dissection of the hepatoduodenal ligament
  - Distal
    - Pancreaticoduodenectomy
    - + lymph node dissection of the hepatoduodenal ligament

- Intrahepatic: as for HCC
  - + lymph node dissection of the hepatoduodenal ligament


(a)
(b)
(c)
(d)

Surgery for pCCA

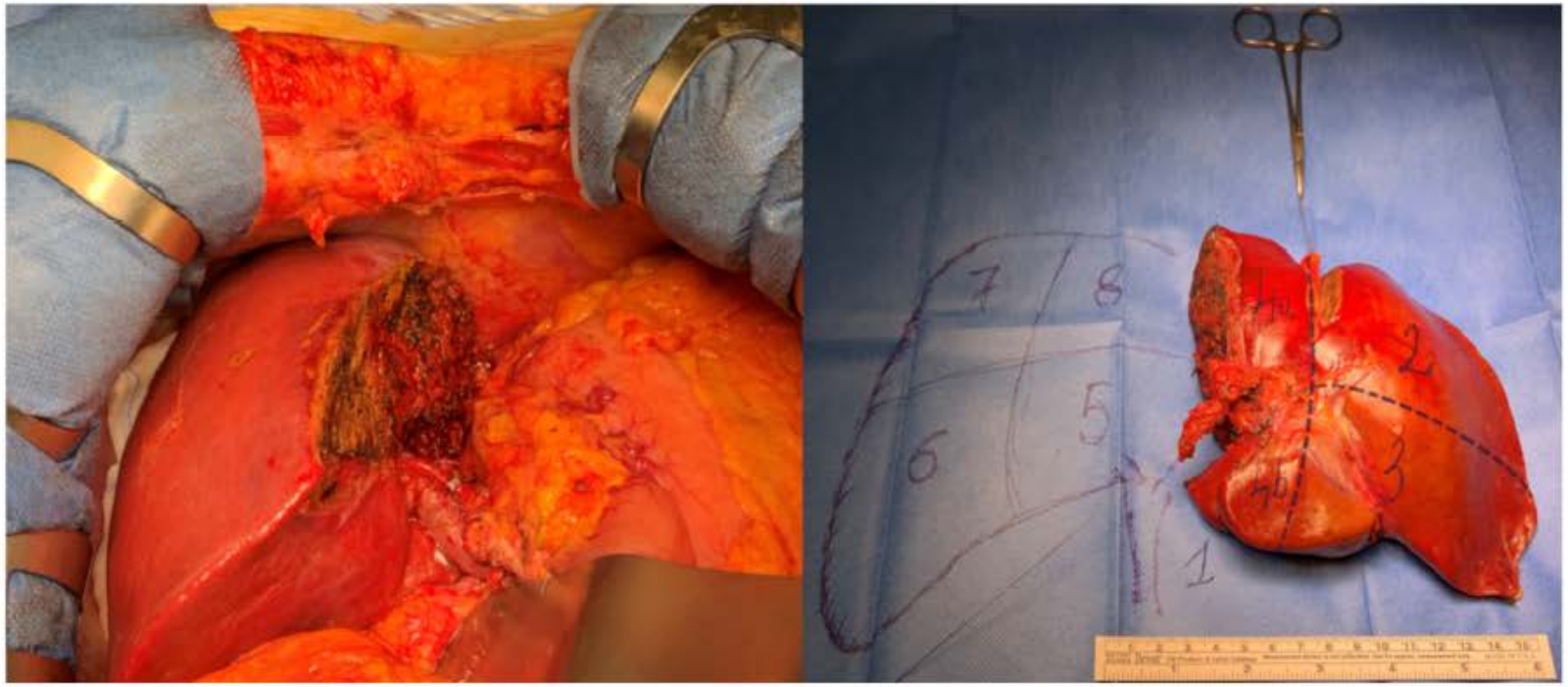
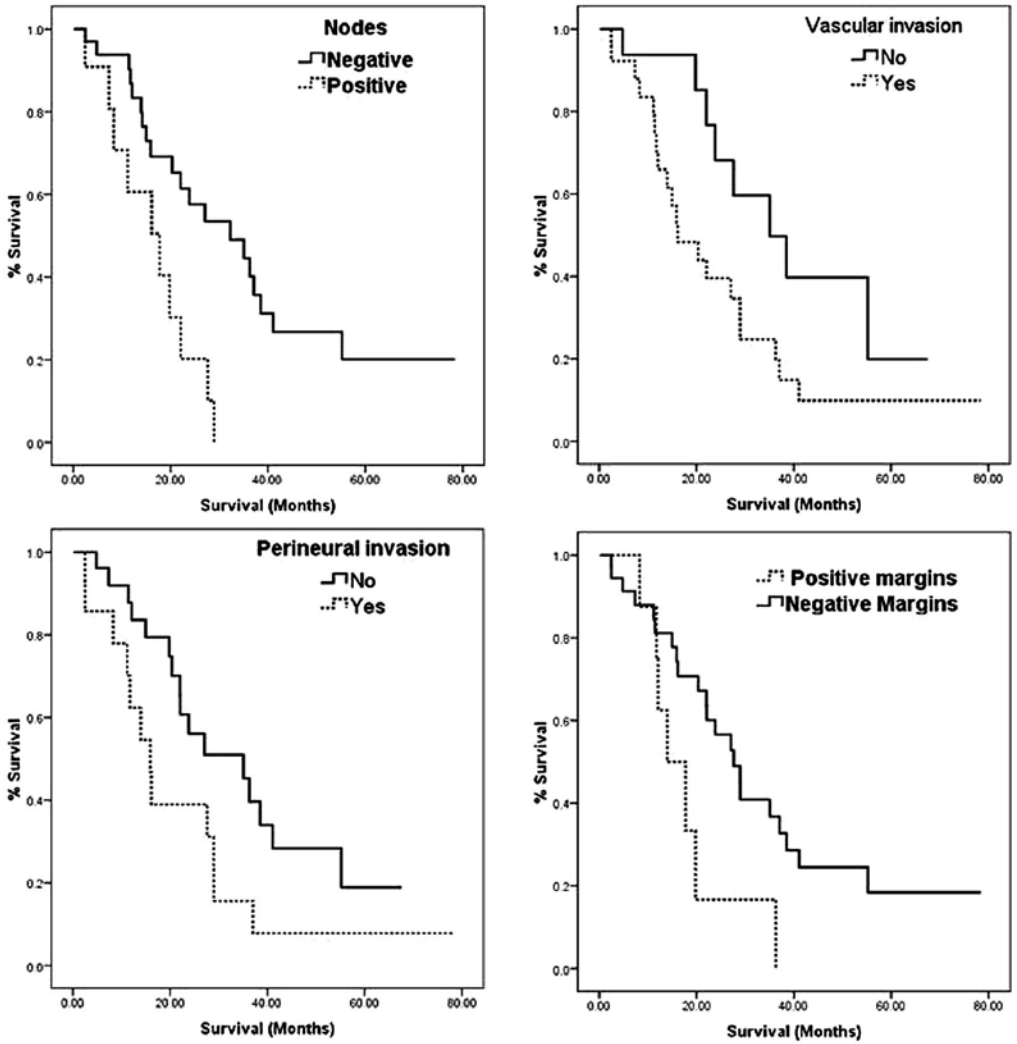


Figure 1. Left hepatectomy with caudate lobe resection for perihilar cholangiocarcinoma (pCCA) (Bismuth IIIb).

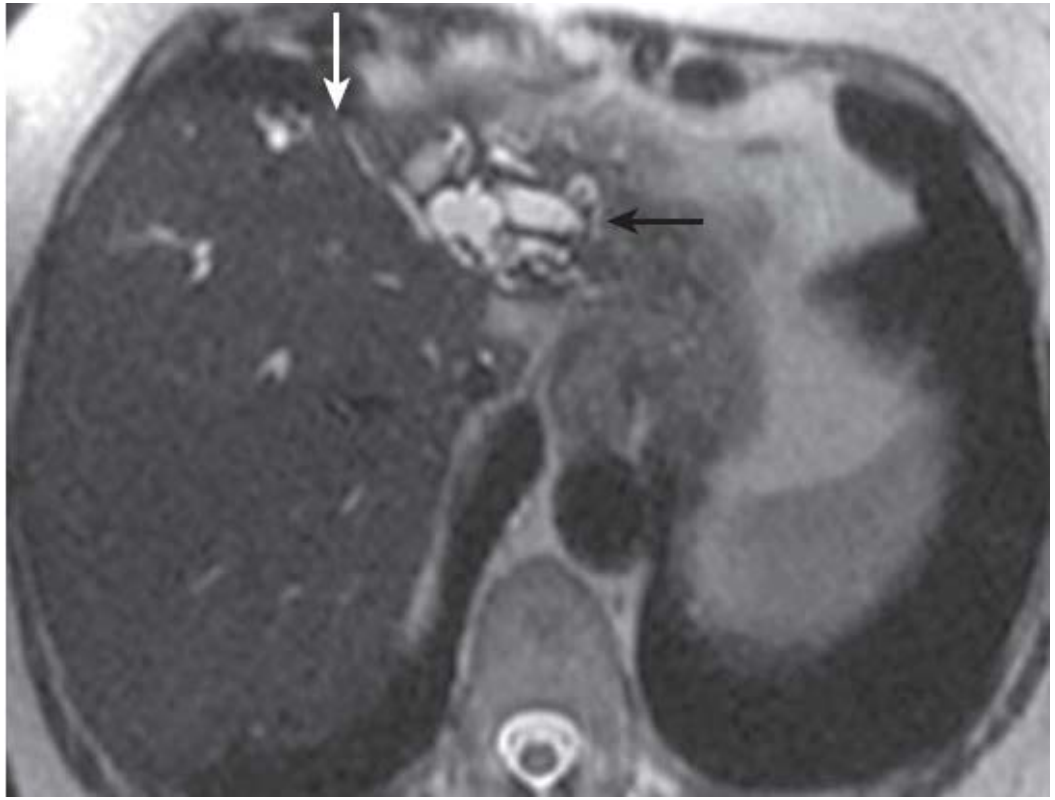
Factors influencing long-term survival

- R0 resection
- number of tumors
- vascular invasion
- lymph node metastases



Unresectability criteria

Medical contraindication to surgical intervention
Advanced cirrhosis or portal hypertension
    Inadequate size of future liver remnant
Bilateral second-order biliary radicle involvement
    Bilateral hepatic artery and/or portal venous branch involvement
    Involvement of unilateral hepatic artery with contralateral ductal spread
Main portal vein involvement or encasement
Lobar atrophy with contralateral second-order biliary radicle involvement
Lobar atrophy with contralateral portal vein involvement
N2 nodal involvement
Distant metastases



Outcomes and prognosis

- Fewer than 50% of patients with perihilar cholangiocarcinoma are able to undergo curative resection. Reported 5-year postoperative survival rates range from approximately 10% to 50%.
- intrahepatic cholangiocarcinoma, reported 3-year survival rates following curative resection with negative margins range from 22% to 66%.
- For patients with distal cholangiocarcinoma, 5-year survival rates following pancreaticoduodenectomy range from 15% to 25% in most reported series.
- Among patients with node-negative disease, 5-year postoperative survival rates as high as 54% have been reported

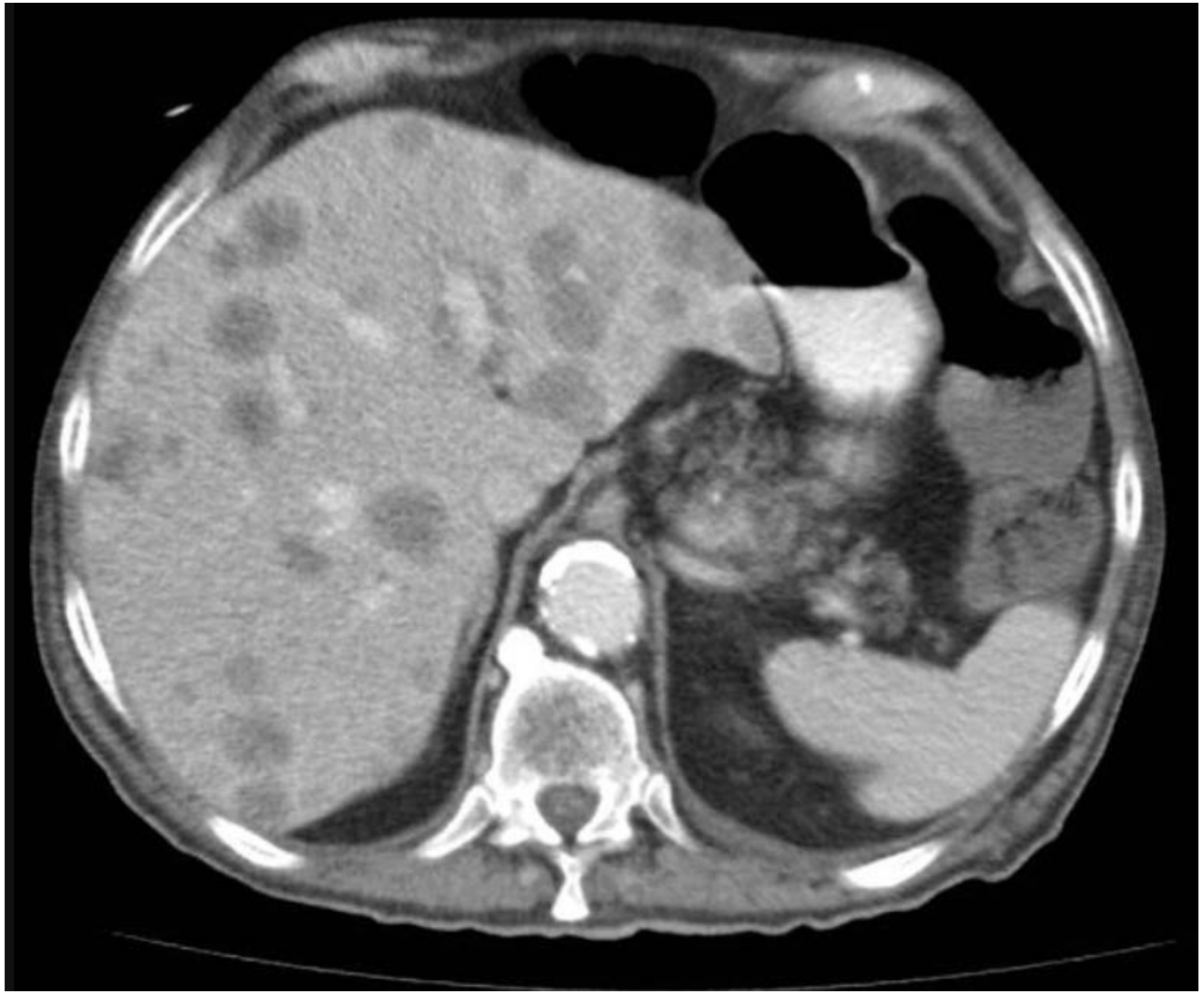
Liver transplant pCCA

Mayo Clinic Protocol	External beam radiation therapy (45 Gy in 30 fractions, 1.5 Gy twice daily) Brachytherapy (20 Gy at 1 cm in approximately 20–25 h)—administered 2 weeks following completion of external beam radiation therapy Capecitabine—administered until the time of transplantation, held during perioperative period for staging Abdominal exploration for staging—as time nears for deceased donor transplantation or day prior to living donor transplantation Liver transplantation
Inclusion Criteria	Diagnosis of pCCA (transcatheter biopsy or brush cytology, CA 19–9 > 100 mg/mL and/or a mass on cross-sectional imaging with a malignant appearing stricture on cholangiography) Unresectable tumor above cystic duct (pancreatoduodenectomy for microscopic involvement of CBD, resectable pCCA arising in PSC) Radial tumor diameter 3 cm Absence of intrahepatic and extrahepatic metastases Candidate for liver transplantation
Exclusion Criteria	Intrahepatic cholangiocarcinoma Uncontrolled infection Prior radiation or chemotherapy Prior biliary resection or attempt resection Intrahepatic metastases Evidence of extrahepatic disease History of other malignancy within 5 years Transperitoneal biopsy (including percutaneous and EUS-guided FNA)

pCCA: perihilar cholangiocarcinoma; PSC: primary sclerosis cholangitis, CA19-9: Carbohydrate Antigen 19-9; CBD: common bile duct; EUS: endoscopic ultrasound; FNA: guided fine-needle aspiration.

- ✓ 5-year recurrence free survival of 65% for Klatskin
- ✓ there is an emerging body of evidence for the efficacy of LT in selected patients with iCCA

CRLM

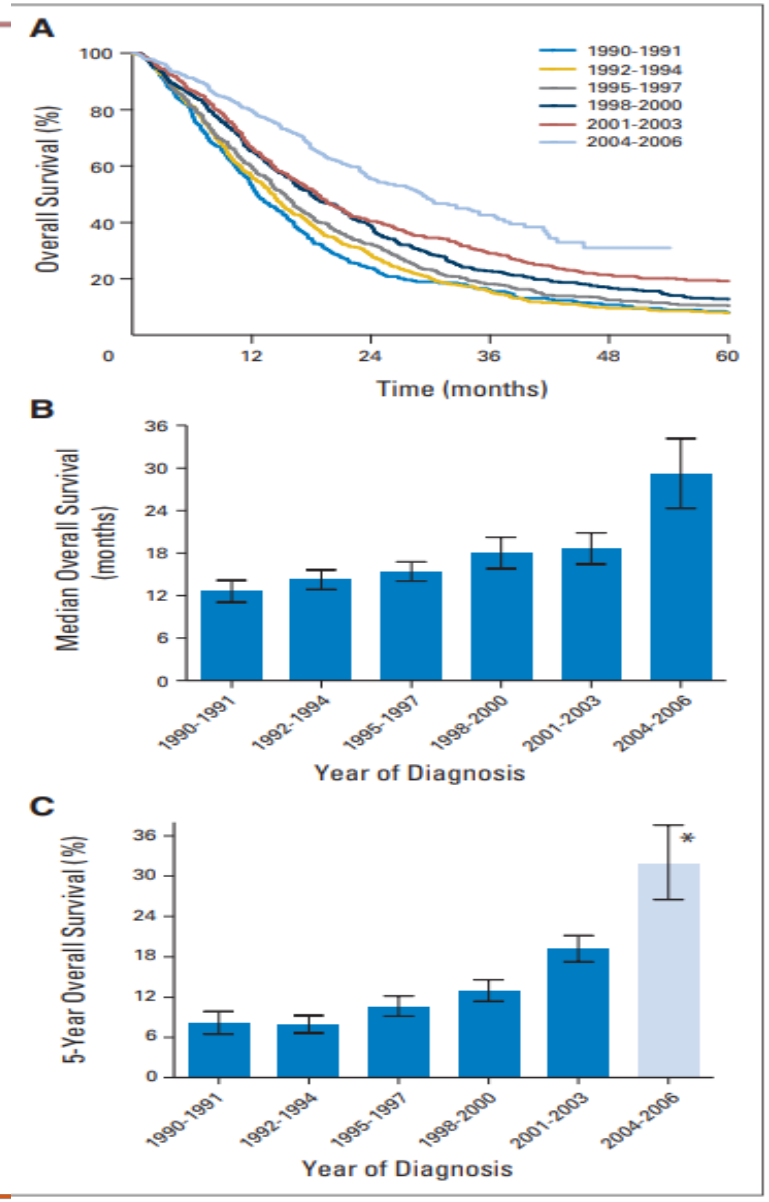


- Hepatic metastases comprise approximately 90% of hepatic malignancies
- Approximately 50% of patients with CRC will develop metastases during their course of disease, and up to 25% will have liver metastases at the time of presentation
- Selected patients undergoing modern chemotherapeutic regimens in combination with complete metastasectomy can achieve durable 5-year survival rates exceeding 50%

TABLE 134.1 Survival Outcomes in Patients With Metastatic Colorectal Cancer Treated With Modern Combined Chemotherapy and Resection

Study	No. of Patients	Initially Resectable	Regimen	Disease-Free Survival	Overall Survival
EORTC 40983[25,26] phase III RCT (EPOC)	152 151	Yes	Surgery FOLFOX + Surgery + FOLFOX	28.1% 36.2% (3 yr) $P = .041$	47.8% 51.2% (5 yr) P = NS
Ychou et al.[28] phase III RCT	153 153	Yes	5-FU + leucovorin FOLFIRI	46% 51% (2 yr) $P = .44$	71.6% 72.7% (3 yr) $P = .69$
Adam et al.[29]	701	No	FOLFOX	NA	34% (5 yr)
Wein et al.[30] phase II trial	20	Yes	FOLFOX	52% (2 yr)	80% (2-yr DSS)
Taieb et al[31] phase II trial	47	Yes	FOLFOX followed by FOLFIRI	47% (2 yr)	89% (2 yr)
Barone et al.[32]	40	No	FOLFIRI	NA	63.5% (2 yr)
Masi et al.[33]	196	No	FOLFOX/FOLFIRI?	29% (5 yr)	42% (5 yr)
First-BEAT trial[34]	107	No	Bev + 5-FU based	NA	89% (2 yr)
N016966 study[34]	34 44	No	Placebo + XELOX/FOLFOX Bev + XELOX/FOLFOX	NA	82.3% 90.9% (2 yr)
New EPOC[27]	117 119	Yes	FOLFOX or XELOX Above regimen + cetuximab	20.5 months 14.1 months (PFS) $P = .03$	NA

BEAT, Bevacizumab Expanded Access Trial; *Bev*, bevacizumab; *DSS*, disease-specific survival; *EORTC*, European Organization for Research and Treatment of Cancer; *FOLFIRI*, 5-fluorouracil, leucovorin, and irinotecan; *FOLFOX*, 5-fluorouracil, leucovorin, and oxaliplatin; *5-FU*, 5-fluorouracil; *NA*, not available or not reported; *NS*, not significant; *PFS*, progression-free survival; *RCT*, randomized controlled trial; *XELOX*, capecitabine and oxaliplatin.



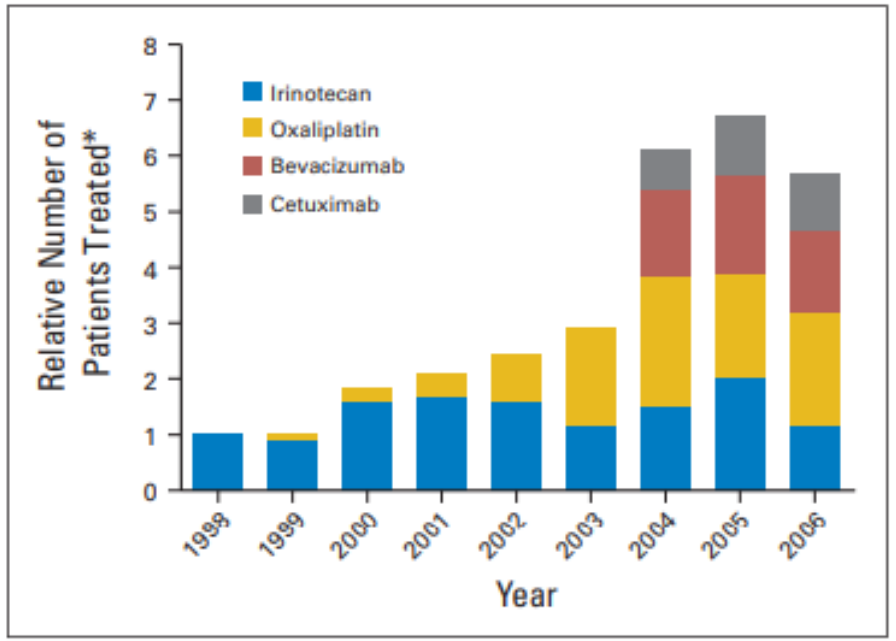


Fig 5. The use of novel chemotherapeutics increased between 1998 and 2006, with a rapid change in 2004. (*) Compared with irinotecan use in 1998 and normalized by yearly patient volume. Details of normalization under Methods.

Kopetz S, Chang GJ, Overman MJ, Eng C, Sargent DJ, Larson DW, Grothey A, Vauthey JN, Nagorney DM, McWilliams RR. Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. J Clin Oncol. 2009 Aug 1;27(22):3677-83.

mCRC

General Prognostic factors

1. Preoperative CE
2. LN status of prir
3. Disease free int
4. Extrahepatic dis
5. Resection margi

Clinical

Five clinical parameters were selected, as criteria for

me prediction.

,

from the primary to
months

umors > 1

vel > 200 ng/ml,

patic tumor > 5 cm,

l for patients with
%, whereas that
points was 14%

Table 54-10 Clinical Risk Score and Survival in 1001 Patients Undergoing Liver Resection for Metastatic Colorectal Cancer*

	Survival Rate (%)			
SCORE	1 YEAR	3 YEAR	5 YEAR	MEDIAN SURVIVAL (MO)
0	93	72	60	74
1	91	66	44	51
2	89	60	40	47
3	86	42	20	33
4	70	38	25	20
5	71	27	14	22

Adapted from Fong Y, Fortner J, Sun RL, et al: Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: Analysis of 1001 consecutive cases. Ann Surg 230:309–318, 1999.

*Each of the following five risk factors equals one point: node-positive primary, disease-free interval <12 months, >one tumor, size >5 cm, carcinoembryonic antigen level >200 ng/mL. Score is total number of points in an individual patient.

Fong et al.Ann Surg. 1999 Sep;230(3):309-18;

TABLE 134.2 Nonsurgical Regional Therapies for Metastatic Colorectal Cancer to the Liver

Treatment Modality	Limitations	Outcomes	Complications
RFA[50]	Higher recurrence compared with resection Lesion proximity to blood vessels Lesion size >5 cm	Up to 84% local recurrence rate Survival benefit not established	Morbidity 5%–30%: abscess, hemorrhage, bile leak
Cryoablation[51]	Similar to RFA, but possible higher rate of complications	Local recurrence rate: 10%–60%	Morbidity 15%–30%: hemorrhage bile leak, cryoshock syndrome, myoglobinuria
HAI[52]	Laparotomy needed to implant infusion device Limited centers with experience	Response rate >50% No proven survival benefit	Hepatobiliary toxicity Pump complications Gastritis/duodenitis
Radioembolization (yttrium 90 microspheres)[53]	Emerging experience	Response rate: 44% Progression-free survival: 16–18 months Combined with systemic chemotherapy or HAI	Morbidity: 24% Abdominal pain and fever Gastritis/duodenitis Radiation hepatitis
Conformal/stereotactic radiotherapy[54]	Low liver tolerance to radiation Lesion proximity to adjacent organs	Median survival: 17 months Local control rates >60%	Radiation hepatitis: 5% Skin erythema Chest wall pain
Irreversible electroporation[55,56]	Emerging experience	NA	Abscess, bile leak

HAI, Hepatic artery infusion; *NA*, not available; *RFA*, radiofrequency ablation.

- In 2006 the AHPBA, SSO, SSAT put the

Indications for hepatectomy for mCRC.

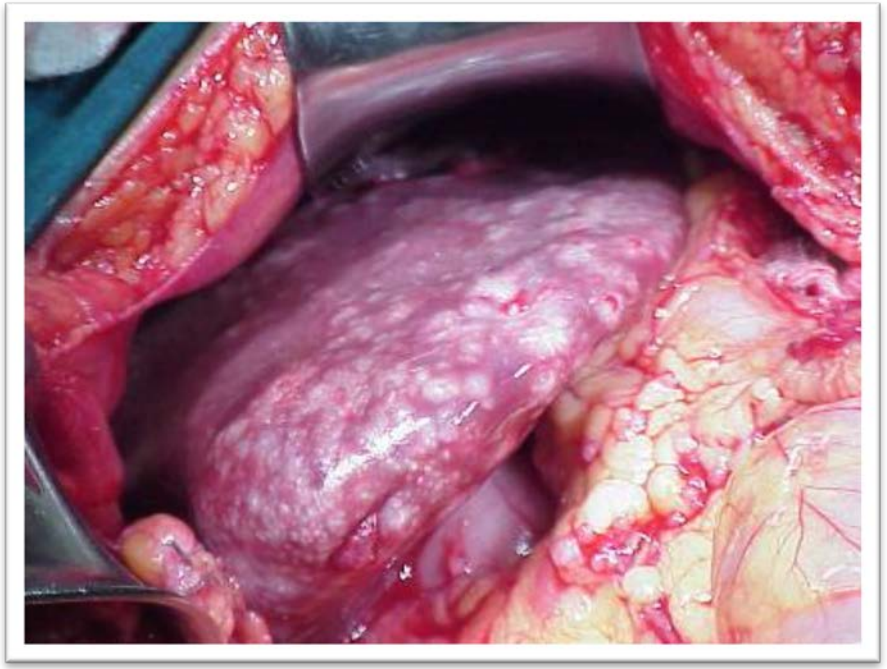
➢ The American consensus suggested CRLMs should be considered resectable if

- (i) the disease can be completely resected (regardless of margin),
- (ii) two adjacent liver segments can be spared with adequate vascular inflow and outflow and biliary drainage,
- (iii) the volume of the liver remaining after resection, i.e. the ‘future liver remnant’ (FLR), will be adequate

Contraindications for Hepatectomy today

- non-treatable primary tumor
- locoregional recurrence
- widespread pulmonary disease
- peritoneal disease
- extensive nodal disease, such as retroperitoneal, mediastinal or portal nodes
- bone or CNS metastases.

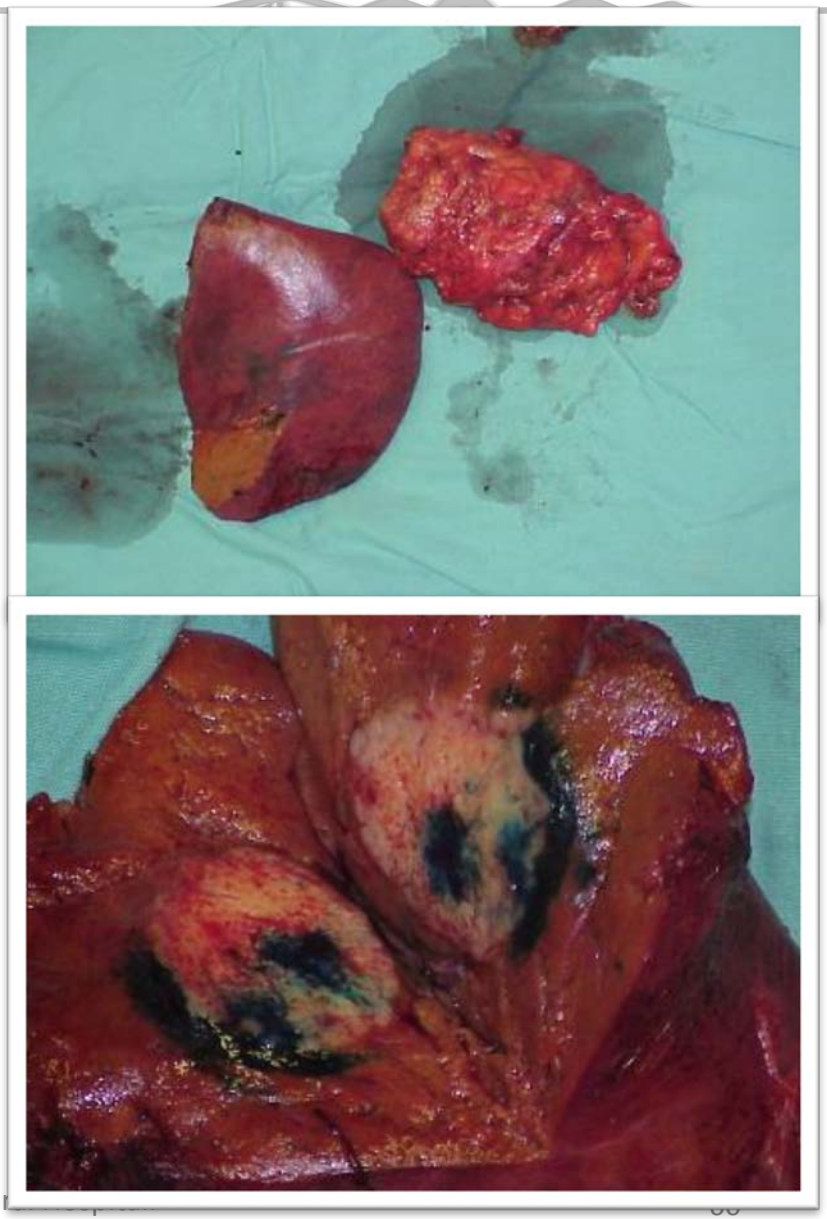
(Category of evidence II; strength of recommendation B)



Garden OJ et al Gut. 2006 Aug;55 Suppl 3:iii1-8

Surgical strategies to improve resectability

- Portal vein embolization
- Two-stage hepatectomy
- Repeat hepatectomy
- Extreme liver surgery
- Extrahepatic colorectal disease

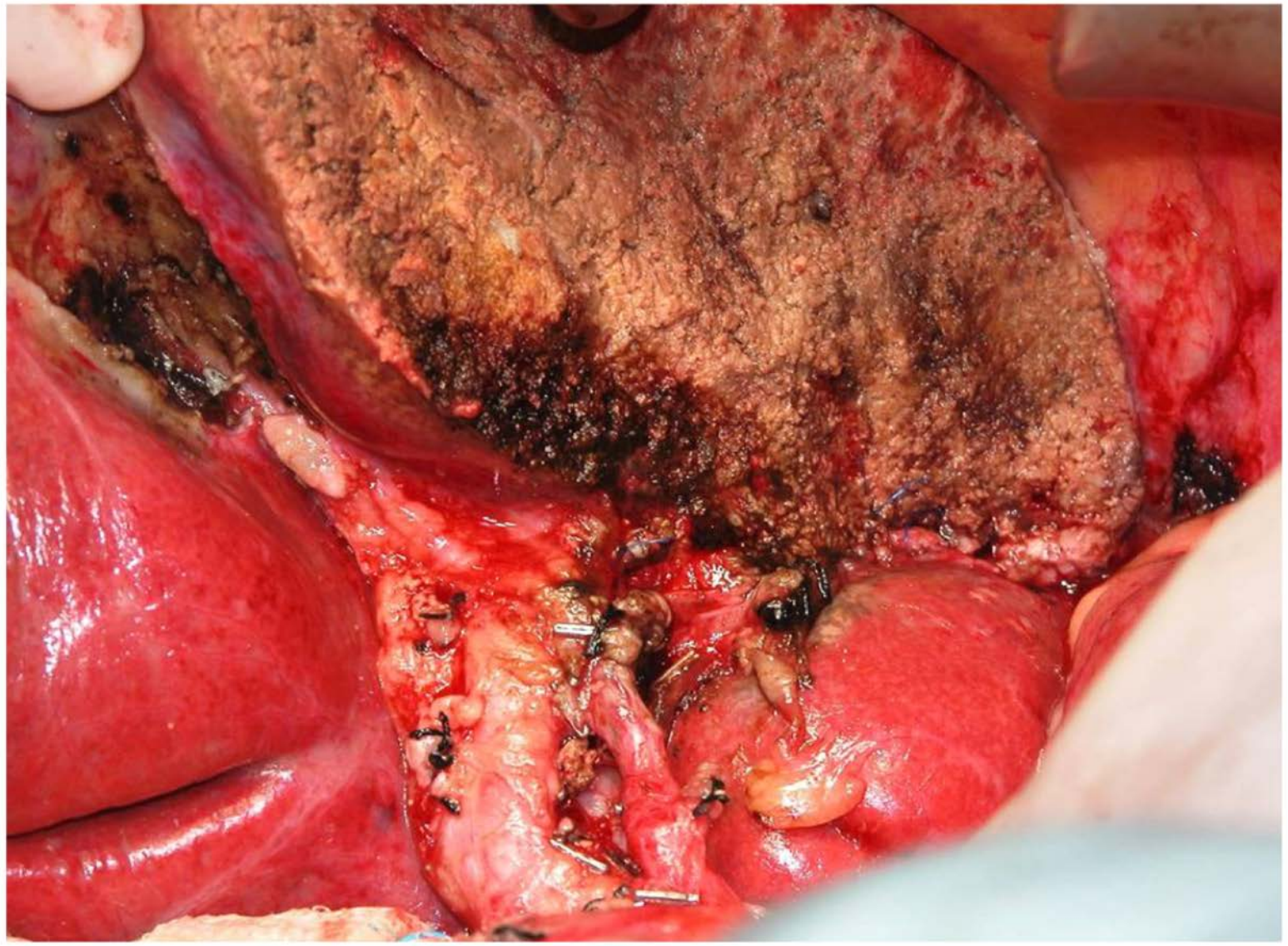


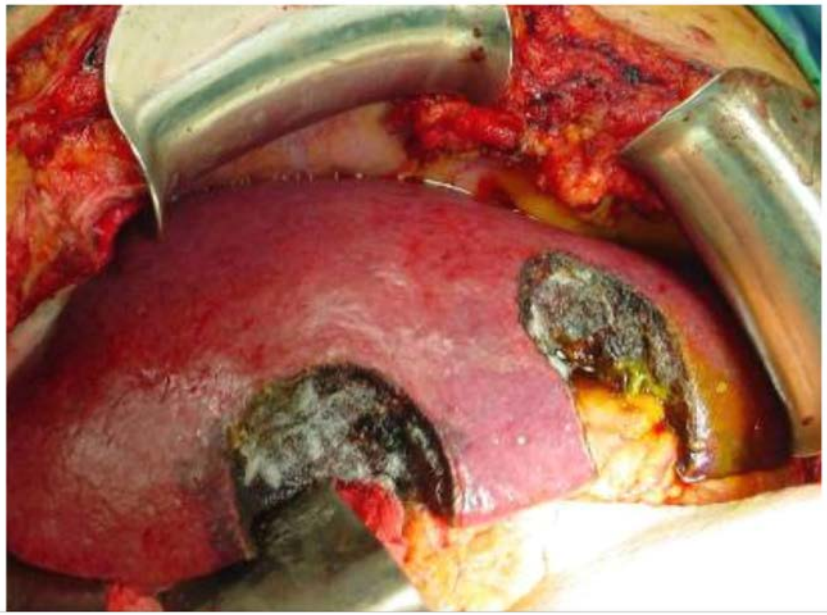
mCRC

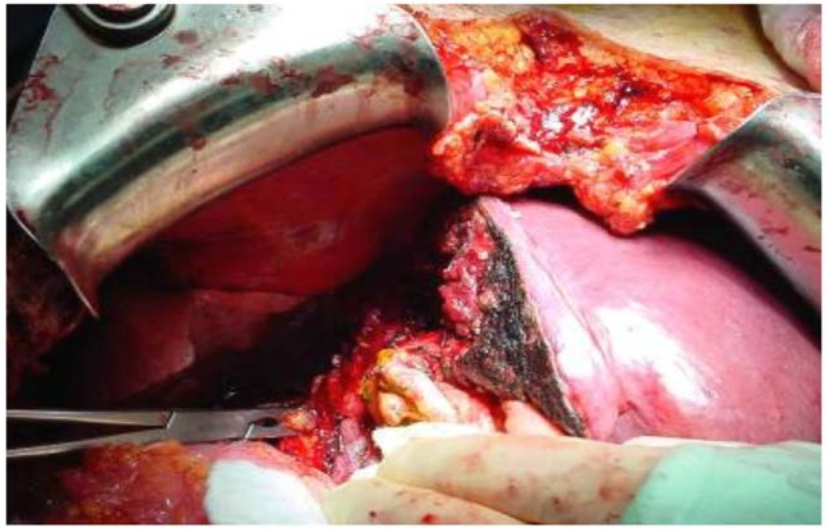
Predicting poorer outcome after resection of colorectal liver metastases

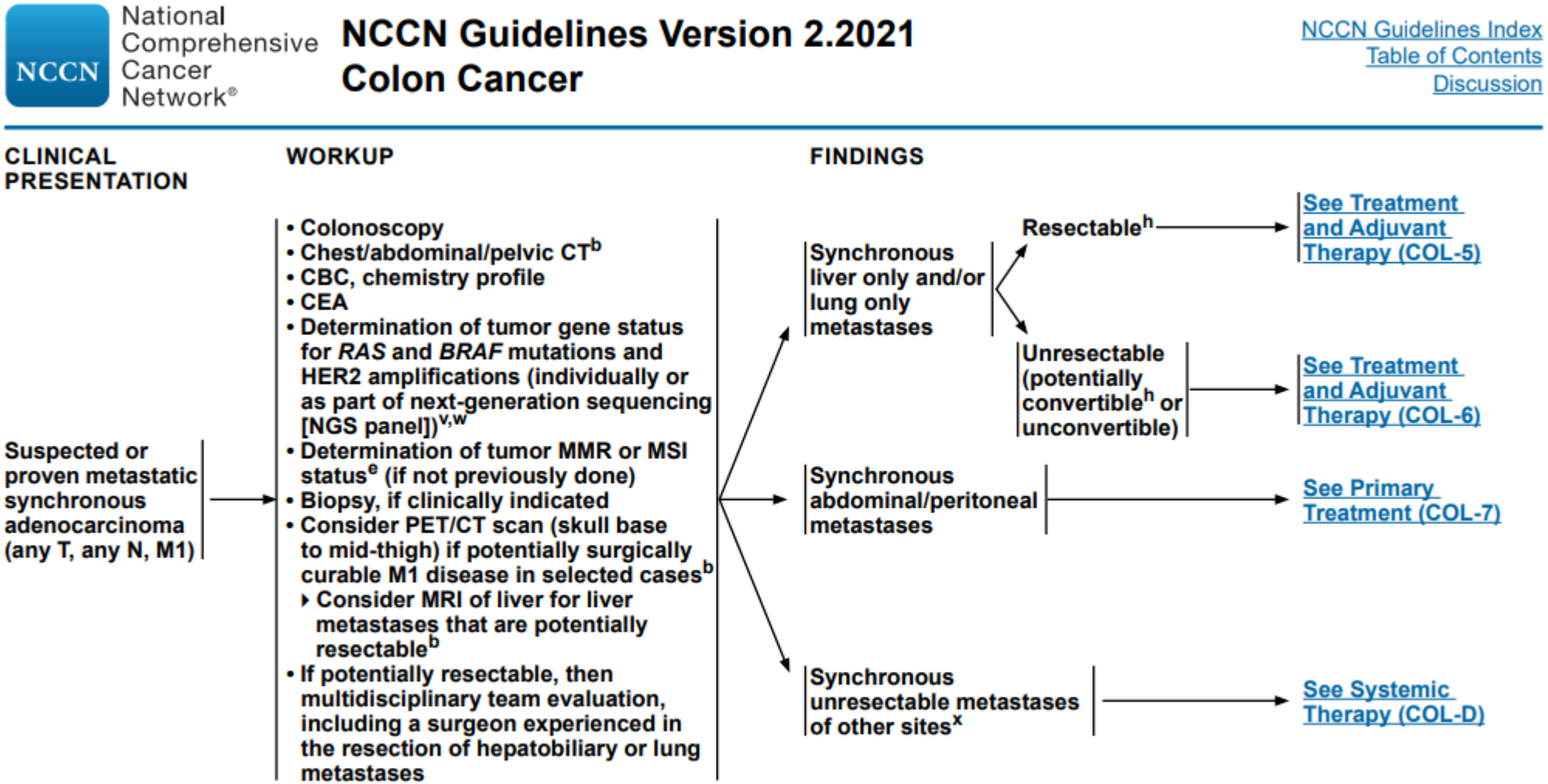
- **Positive resection margin**
- Extrahepatic disease
- Node positive (stage 3) primary colorectal cancer
- Disease free interval from primary tumour <1 year
- Largest metastasis >5 cm
- Number of metastases >1
- CEA >200 ng/ml
- Age of patient

Nordlinger et al. Cancer 1996; 77: 1254-62
Fong et al. Annals of Surgery 1999; 230: 309-15





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NCCN Guidelines Version 2.2021
Colon Cancer
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FINDINGS
Suspected or proven metastatic synchronous adenocarcinoma (any T, any N, M1)
• Colonoscopy
• Chest/abdominal/pelvic CT[b]
• CBC, chemistry profile
• CEA
• Determination of tumor gene status for RAS and BRAF mutations and HER2 amplifications (individually or as part of next-generation sequencing [NGS panel])[v,w]
• Determination of tumor MMR or MSI status[e] (if not previously done)
• Biopsy, if clinically indicated
• Consider PET/CT scan (skull base to mid-thigh) if potentially surgically curable M1 disease in selected cases[b]
▸ Consider MRI of liver for liver metastases that are potentially resectable[b]
• If potentially resectable, then multidisciplinary team evaluation, including a surgeon experienced in the resection of hepatobiliary or lung metastases
Synchronous liver only and/or lung only metastases
Resectable[h]
See Treatment and Adjuvant Therapy (COL-5)
Unresectable (potentially convertible[h] or unconvertible)
See Treatment and Adjuvant Therapy (COL-6)
Synchronous abdominal/peritoneal metastases
See Primary Treatment (COL-7)
Synchronous unresectable metastases of other sites[x]
See Systemic Therapy (COL-D)

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Colon Cancer

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Discussion

TREATMENT
Resectable[h] synchronous liver and/or lung metastases only

ADJUVANT TREATMENT[b] (UP TO 6 MO PERIOPERATIVE TREATMENT)
(resected metastatic disease)

Synchronous or staged colectomy[y] with liver or lung resection (preferred) and/or local therapy[z]
or
Neoadjuvant therapy (for 2–3 months) FOLFOX (preferred) or CAPEOX (preferred) or FOLFIRI (category 2B) or FOLFOXIRI (category 2B) followed by synchronous or staged colectomy[y] and resection of metastatic disease
or
Colectomy,[y] followed by chemotherapy (for 2–3 months) FOLFOX (preferred) or CAPEOX (preferred) or FOLFIRI (category 2B) or FOLFOXIRI (category 2B) and staged resection of metastatic disease

→ **FOLFOX (preferred) or CAPEOX (preferred)**
or
Capecitabine or 5-FU/leucovorin → See Surveillance (COL-8)

or
Consider ([Nivolumab ± ipilimumab] or pembrolizumab [preferred]) (dMMR/MSI-H only)[aa] followed by synchronous or staged colectomyy and resection of metastatic disease → See Surveillance (COL-8)

Approach to CRLM

- **Simultaneous**:

Liver metastases and the primary tumor are resected in the same operation (Vogt, 1991)

- **Sequential bowel-first**:

First resection of the CRC and then the liver metastases.

With or without Chemo during the interval

- **Sequential liver first (reverse approach):**

Resection first of all liver metastases after preoperative chemotherapy and later the CRC (Mentha G, 2006)

✓ Rationale1 : the lesion that kills the patient is the metastasis

✓ Rationale 2: metastases usually determine resectability

✓ Rationale 3:progression of the CRLM during treatment of the primary tumour

Is there a difference?

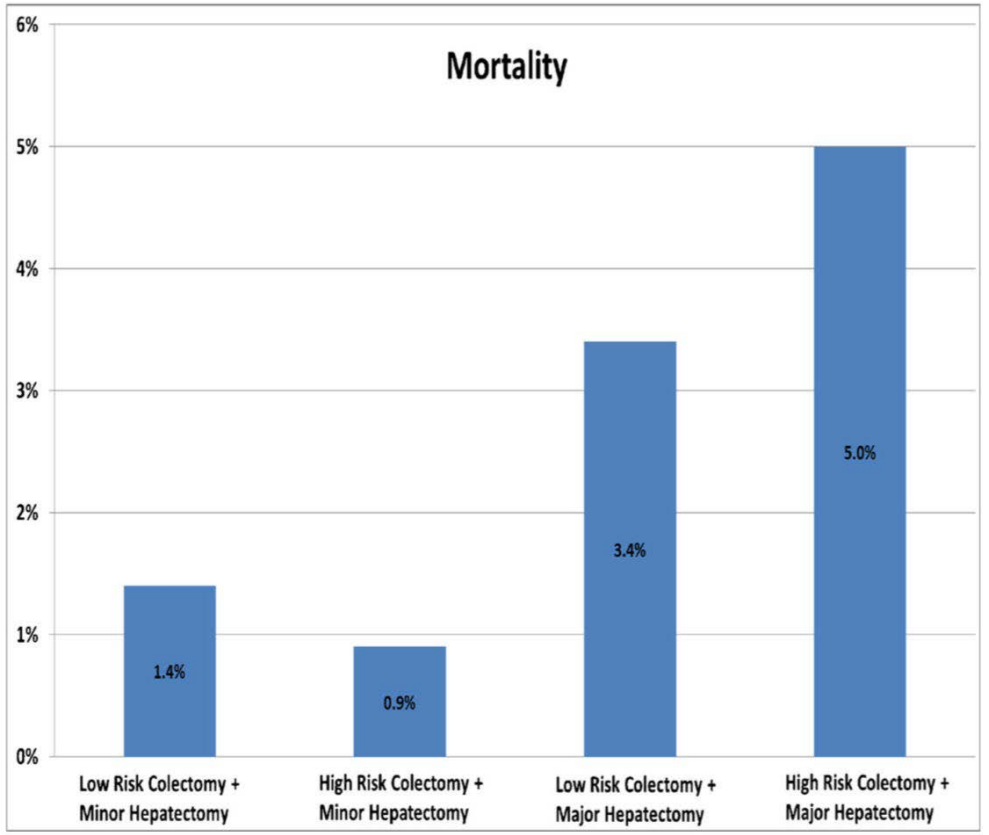
	Sequential Colon first N= 72	Simultaneous Colon & Liver N= 43	Sequential Liver first N= 27	
Morbidity	51 %	47 %	31 %	p NS
Mortality	3 %	5 %	4 %	p NS
Survival (5 years)	**48 %**	**55 %**	**39 %**	**p NS**
Nº M1	3	1	4	p < 0.05
Major Hepatectomy	66 %	35 %	89 %	p< 0.05

Brouquet A, Mortenson MM, Vauthey J-N et al. Surgical Strategies for Synchronous Colorectal Liver Metastases in 156 Consecutive Patients: Classic, Combined or Reverse Strategy? J Am Coll Surg **2010**; 210: 934-941

Careful patient selection is necessary

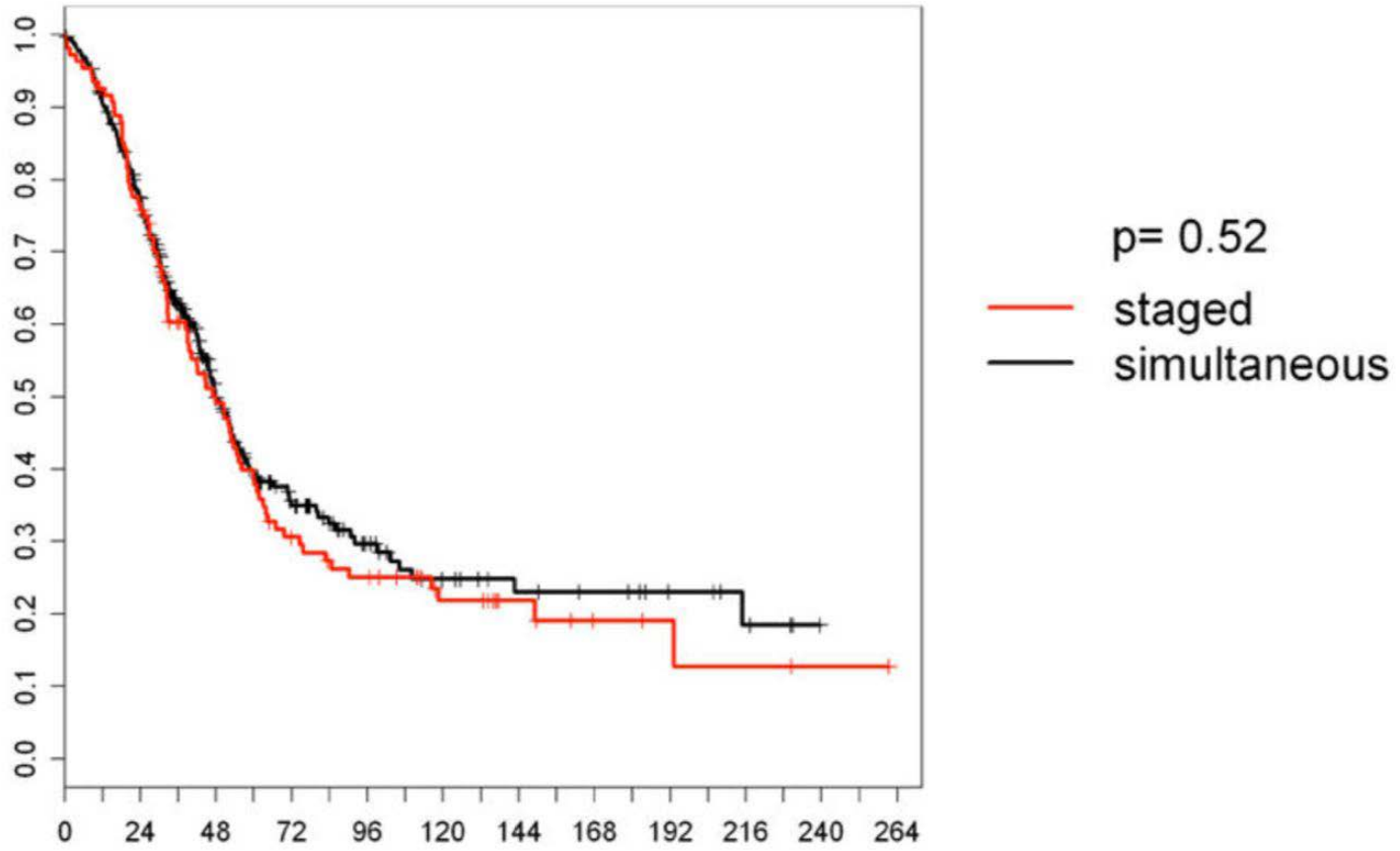
A NSQIP Review of Major Morbidity and Mortality of Synchronous Liver Resection for Colorectal Metastasis Stratified by Extent of Liver Resection and Type of Colorectal Resection

Christopher R. Shubert[1,2] · Elizabeth B. Habermann[2] · John R. Bergquist[1,2] Cornelius A. Thiels[1,2] · Kristine M. Thomsen[2] · Walter K. Kremers[2] · Michael L. Kendrick[1] · Robert R. Cima[2,3] · David M. Nagorney[1]



Long-term oncologic outcomes for simultaneous resection of synchronous metastatic liver and primary colorectal cancer

Gerd R. Silberhumer MD [a, d], Philip B. Paty MD [a], Brian Denton MS, MA [c], Jose Guillem MD [a], Mithat Gonen MD [c], Raphael L.C. Araujo MD, PhD [b], Garret M. Nash MD [a], Larissa K. Temple MD [a], Peter J. Allen MD [b], Ronald P. DeMatteo MD [b], Martin R. Weiser MD [a], W. Douglas Wong MD [a], William R. Jarnagin MD [b], Michael I. D'Angelica MD [b], Yuman Fong MD [e]



Outcome of interest	Number of studies	Number of patients (Simult/Delayed)	Statistical method, estimated effect, (95%CI)	p-value	I^2 (%)
Operating time[13–15,19,22,23,37] (minutes)	7	286/452	MD = 11.04 (–5.04, 27.13)	0.181	95
Blood Losses[16,27,28,30–32,34,40]	9	479/734	SMD = –0.23 (–0.70, 0.24)	0.343	93
Major morbidity Clavien-Dindo III-IV[14–16,19–24,27–38,40]	21	1431/2728	OR = 1.08 (0.91, 1.28)	0.383	56
Wound Infections[14,15,19,22,23,30,32,36,37]	10	549/998	Peto OR = 1.17 (0.72,1.89)	0.531	0
Subphrenic/Perihepatic Abscesses[15,19,22,27,32]	5	302/588	OR = 1.34 (0.76, 2.37	0.313	0
Bile leak/biloma[12,15,19,22,23,30–33,36]	10	504/958	Peto OR = 0.70 (0.43, 1.14)	0.151	0
Hepatic Insufficiency/Failure[23,2732,33,37]	5	340/379	Peto OR = 0.77 (0.45,1.31)	0.342	45
Abdominal/Pelvic abscesses[15,22,27,31,32,36,37]	7	449/689	Peto OR = 1.15 (0.67, 2.00)	0.613	0
Anastomotic Leak[15,19,32,33,36,37]	6	354/708	Peto OR = 1.51 (0.76, 3.00)	0.243	0
Perioperative mortality[12,14–16,18–20,23,24,27–30,32–38]	20	1313/2606	Peto OR = 1.37 (0.83, 2.24)	0.221	55
MD of Length of stay[12–16,19,20,22–24,27–30,32,37–40] (days)	13	883/915	MD = –6.27 (–8.20, –4.34)	<0.001	94
SMD of Length of stay[12–16,19,20,22–25,27–30,32,37–40]	13	883/915	SMD = –1.36 (–2.04, –0.67)	<0.001	97
Long-term OS[12–16,20–23,28,30,33–35,37,39,40]	17	1253/1604	HR = 0.97 (0.88, 1.08)	0.601	0
Long-term OS NOS > 7[13,15,16,21–23,28,30,33–35,39,40]	13	1096/1403	HR = 0.98 (0.88, 1.09)	0.751	0

Gavriilidiset al. Simultaneous versus delayed hepatectomyfor synchronous colorectal liver metastases: a systematic review and meta-analysis. HBP 2018.

Summary Scientific Evidence

- No differences in survival... ... in selected cases
- No differences in complications… … in selected cases
- **Simultaneous**: shorter length of hospital stay and lower costs
- **Liver first approach**: severe liver disease and asymptomatic primary tumour

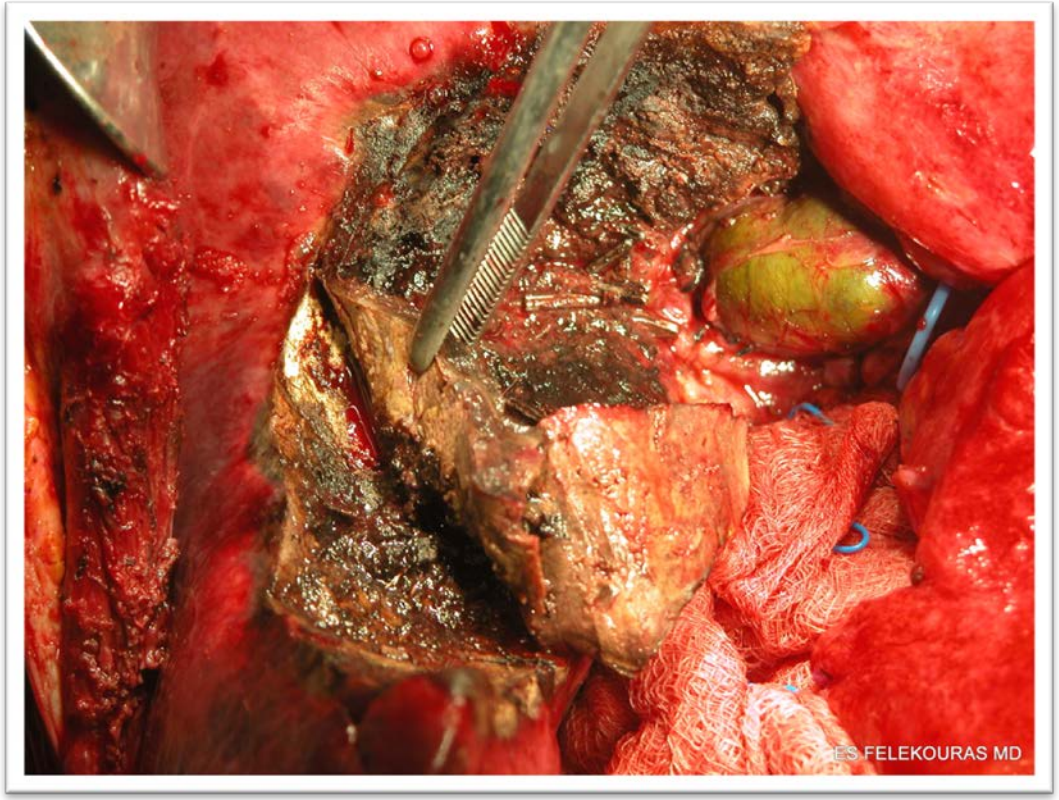
- **Simultaneous approach**

✓Patients fit for surgery

✓“Easy” hepatic resection

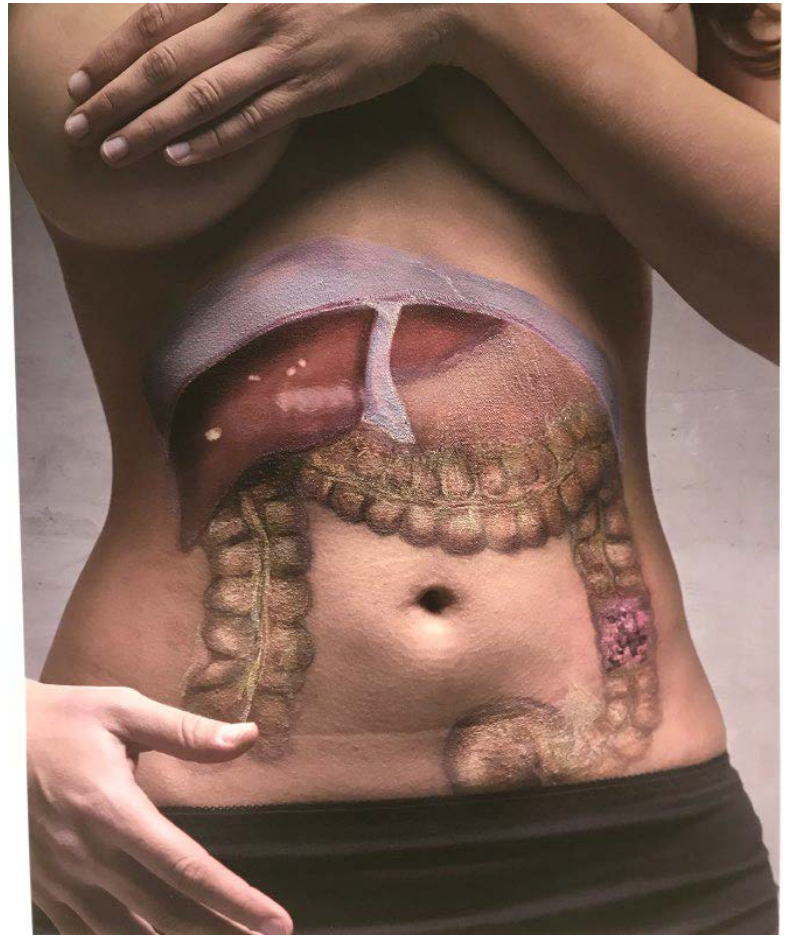
✓Uncomplicated primary tumor

✓Specialized surgeons



- SEQUENTIAL COLON FIRST Surgery

- Symptomatic CRC
- Patient not fit for simultaneous
- Surgeon not an expert in liver surgery
- Doubtful resectabilityof CCR
- Complex surgery of the CRC and the M1



- **LIVER FIRST Surgery**

✓Asymptomatic primary tumor

✓Unresectable or borderline resectable liver M1

✓Risk of M1 progression during treatment of the primary

Summary

- Multidisciplinary treatment strategies
- Selection of patients
- Planification for an appropriate timing
- Complex surgical procedures requiring surgical expertise