UNIVERSITA' DEGLI STUDI DI PERUGIA
DIPARTIMENTO DI MEDICINA E CHIRURGIA
CLMMC V anno
Patologia Sistemica VI (M-Z)
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Liver cancer

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Testo consigliato Harrison's Principles of Internal Medicine – 19-20° Ed.

Liver tumors

Benign liver tumors

- **Hepatocyte**

Adenoma

Multiple adenomatosis

Focal nodular hyperplasia

Nodular regenerative hyperplasia

- **Non Epithelial**

Mesenchymal-

Angioma- hemangioma

Angiomyolipoma

Malignant liver tumor

Primary tumors

- **Hepatocytes**

Hepatocarcinoma

- **Bile duct cells**

Cholangiocarcinoma

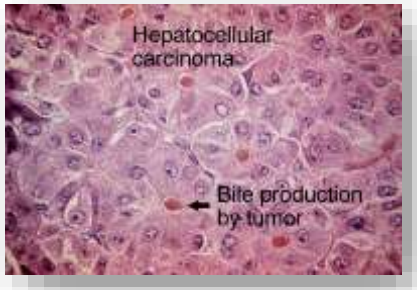
Secondary tumors

Liver metastasis from any solid tumor

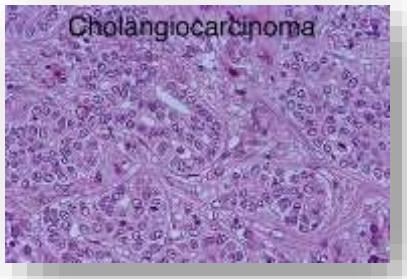
Malignat liver tumors

- **Primary**

  Hepatocellular carcinoma (HCC)



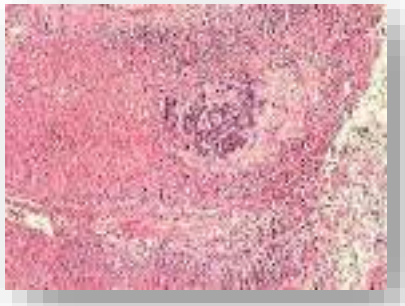
  Cholangiocarcinoma

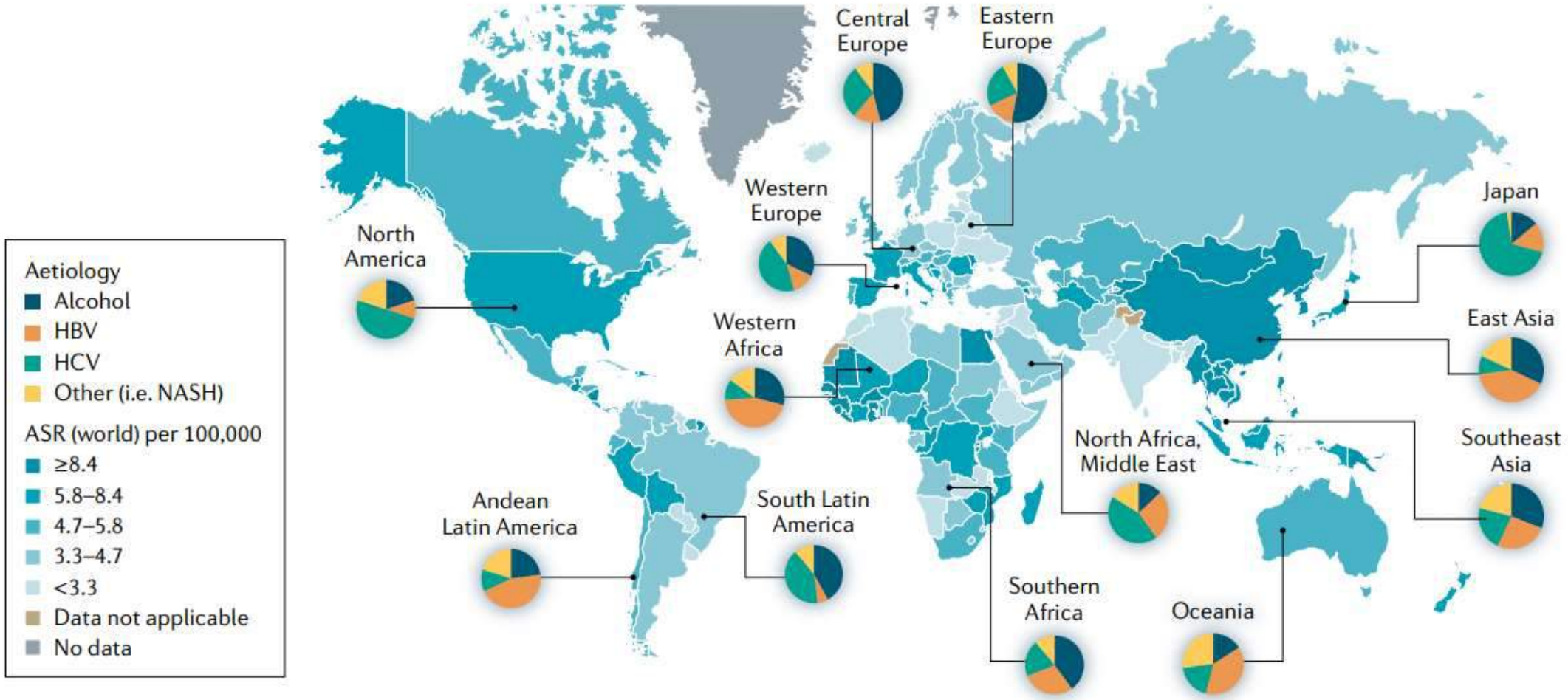


- **Secondary**

  metastasis from stomach,

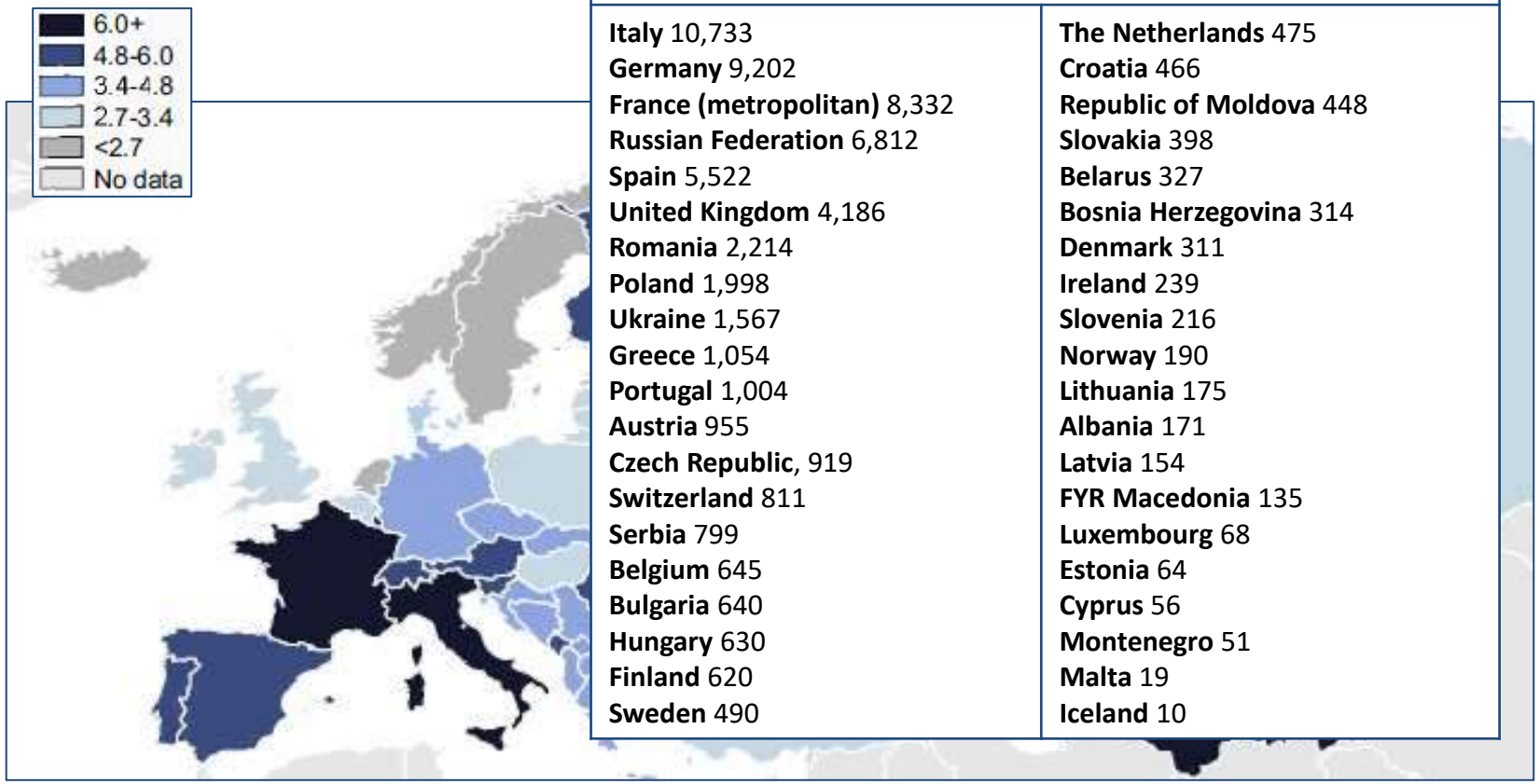
  colon, pancreas, kidney..




Aetiology
Alcohol
HBV
HCV
Other (i.e. NASH)
ASR (world) per 100,000
≥8.4
5.8–8.4
4.7–5.8
3.3–4.7
<3.3
Data not applicable
No data
North America
Central Europe
Eastern Europe
Western Europe
Japan
Western Africa
East Asia
North Africa, Middle East
Southeast Asia
Andean Latin America
South Latin America
Southern Africa
Oceania

Incidence of primary liver cancer in Europe

Incidence rates per 100,000



Total number per country	
Italy 10,733	**The Netherlands** 475
Germany 9,202	**Croatia** 466
France (metropolitan) 8,332	**Republic of Moldova** 448
Russian Federation 6,812	**Slovakia** 398
Spain 5,522	**Belarus** 327
United Kingdom 4,186	**Bosnia Herzegovina** 314
Romania 2,214	**Denmark** 311
Poland 1,998	**Ireland** 239
Ukraine 1,567	**Slovenia** 216
Greece 1,054	**Norway** 190
Portugal 1,004	**Lithuania** 175
Austria 955	**Albania** 171
Czech Republic, 919	**Latvia** 154
Switzerland 811	**FYR Macedonia** 135
Serbia 799	**Luxembourg** 68
Belgium 645	**Estonia** 64
Bulgaria 640	**Cyprus** 56
Hungary 630	**Montenegro** 51
Finland 620	**Malta** 19
Sweden 490	**Iceland** 10

EASL CPG HCC. J Hepatol 2018; doi: 10.1016/j.jhep.2018.03.019

Main risk factors for primary liver cancer worldwide*

- ~90% of HCCs are of known underlying aetiology[1]
  - **Most frequently HCV, HBV, alcohol a**

	Alcohol (%)	HBV (%)	HCV (%)	Others (%)
Europe				
Western	32	13	44	10
Central	46	15	29	10
Eastern	53	15	24	8
North America	37	9	31	23
Andean Latin America	23	45	12	20
Asia				
East Asia	32	41	9	18
Asia-Pacific	18	22	55	6
South-East Asia	31	26	22	21
Africa				
North Africa, Middle East	13	27	44	16
Southern (sub-Saharan)	40	29	20	11
Western (sub-Saharan)	29	45	11	15

*Contribution of hepatitis B, C, alcohol and other causes on absolute liver cancer deaths, both sexes, globally and by region 2015. Data refer to all primary liver cancers (HCC, intrahepatic CCA and liver cancer of mixed differentiation)

1. Akinyemiju T, et al. JAMA Oncol 2017;3:1683–91;
EASL CPG HCC. J Hepatol 2018; doi: 10.1016/j.jhep.2018.03.019

Hepatocarcinoma (HCC)

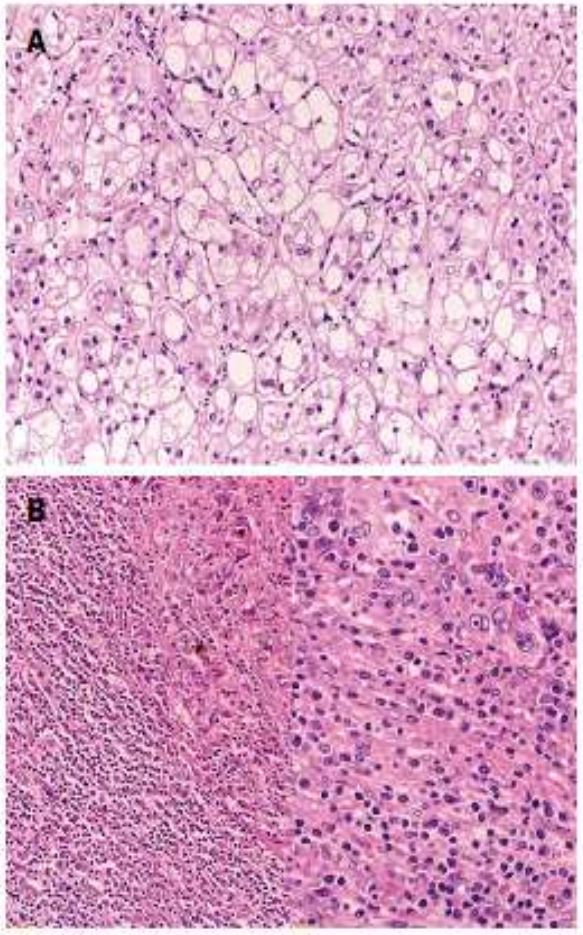
- Hepatocellular carcinoma (HCC) is a primary malignancy of hepatocytes causing approx. 1 ml deaths/year worldwide.
- Hepatocellular carcinoma arises in
- **80-90% of case in the setting of cirrhosis**, appearing 20-30 years following the initial insult to the liver.
- However, 10% of patients have no history or risk factors for the development of cirrhosis.
- The extent of hepatic dysfunction limits treatment options, and as many patients die of liver failure as from tumor progression.

Surveillance Recommendations

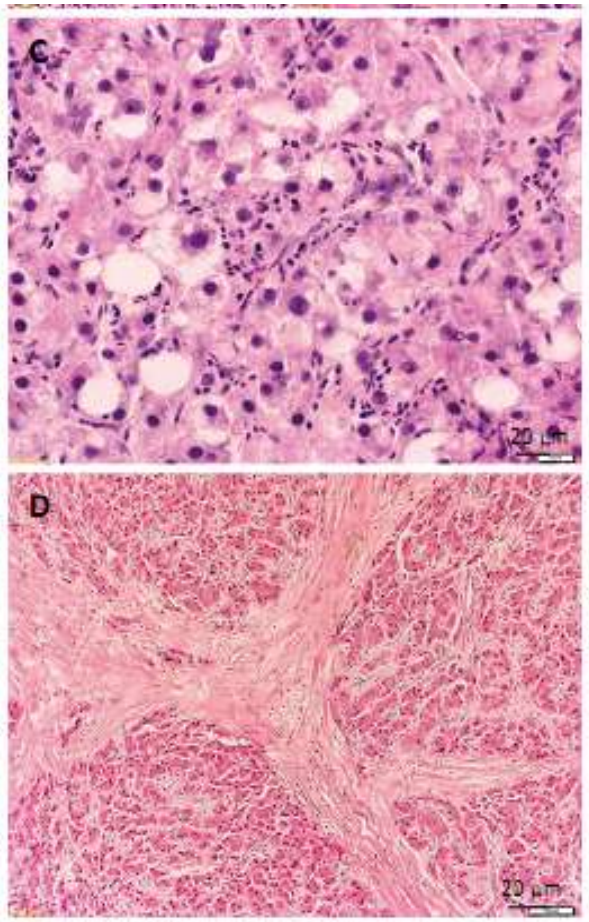
- The target population for surveillance are those with liver cirrhosis (and HBV-infected patients)
- AFP and US are the recommended screening tests for HCC in patients at the highest risk
- Based on tumor doubling time and studies, the recommended interval for surveillance is every 6 months in patients with cirrhosis
- Screening increases likelihood of HCC diagnosis
  - Small and potentially treatable
  - May reduce mortality

Pathology of Hepatocellular Carcinoma

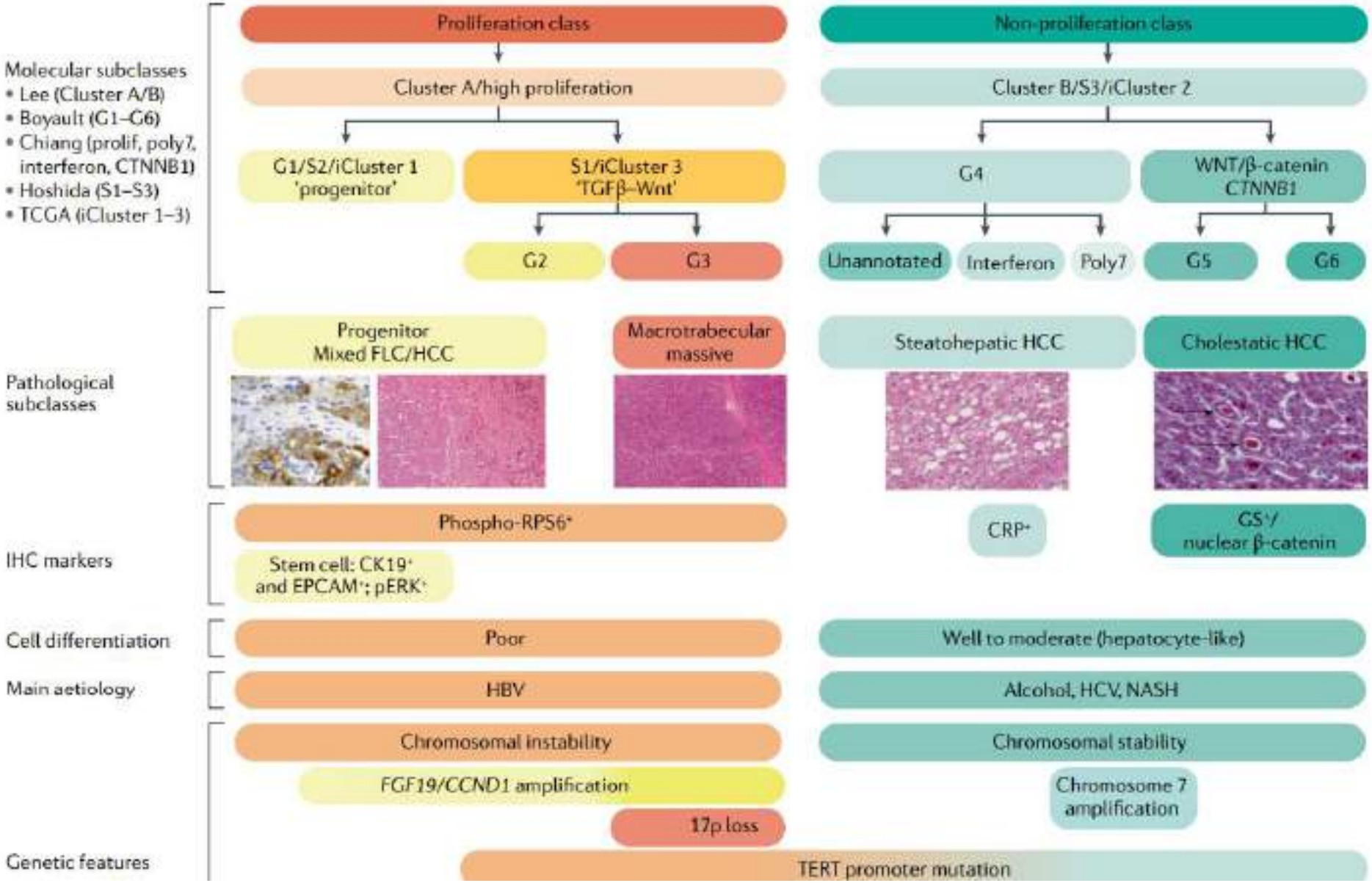
HCC well differentiated

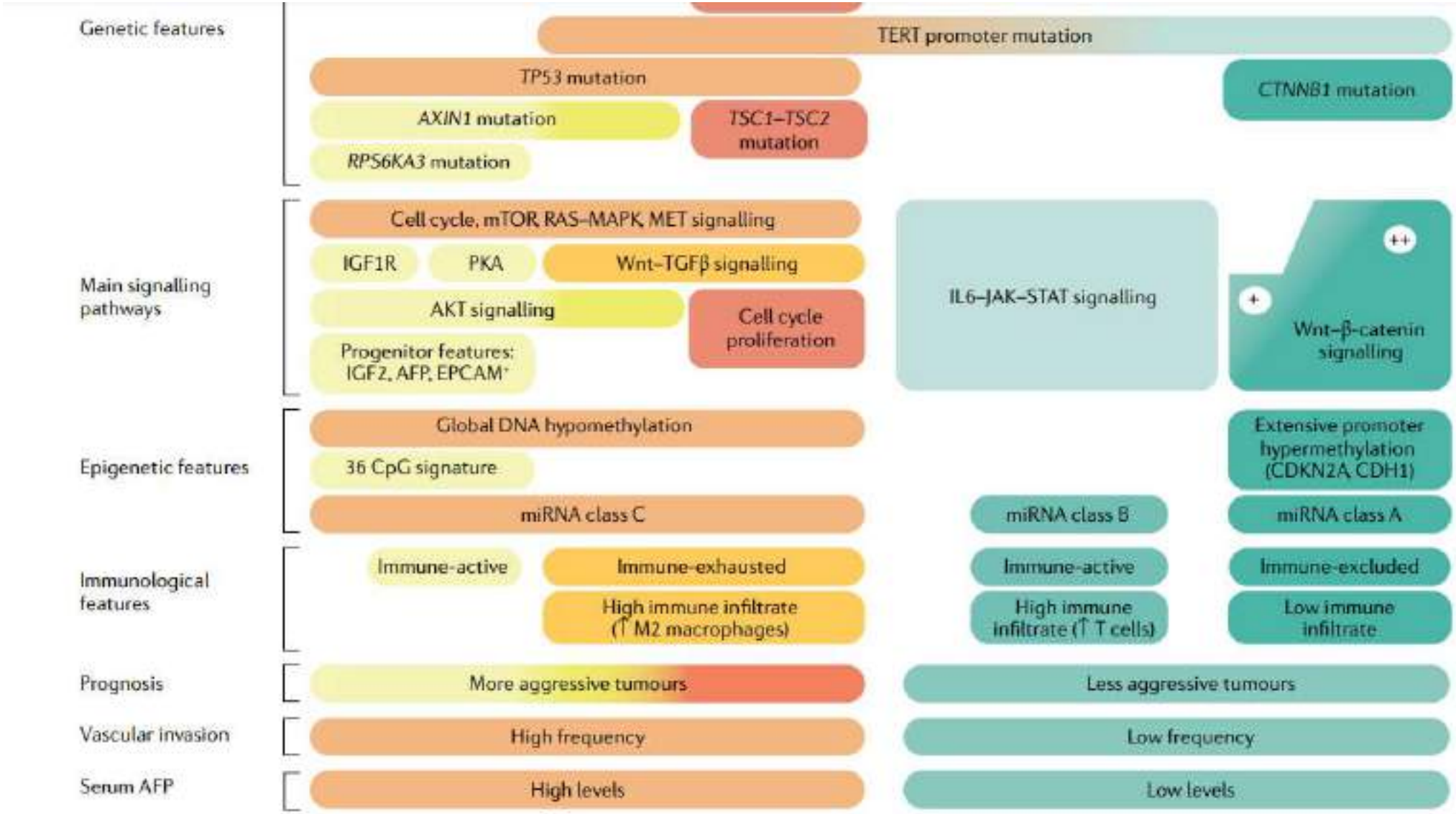


HCC poorly differentiated



HCC fibrolamellar 1


Molecular subclasses
• Lee (Cluster A/B)
• Boyault (G1–G6)
• Chiang (prolif, poly7, interferon, CTNNB1)
• Hoshida (S1–S3)
• TCGA (iCluster 1–3)
Proliferation class
Non-proliferation class
Cluster A/high proliferation
Cluster B/S3/iCluster 2
G1/S2/iCluster 1 'progenitor'
S1/iCluster 3 'TGFβ–Wnt'
G4
WNT/β-catenin CTNNB1
G2
G3
Unannotated
Interferon
Poly7
G5
G6
Pathological subclasses
Progenitor Mixed FLC/HCC
Macrotrabecular massive
Steatohepatic HCC
Cholestatic HCC
IHC markers
Phospho-RPS6+
Stem cell: CK19+ and EPCAM+; pERK+
CRP+
GS+/ nuclear β-catenin
Cell differentiation
Poor
Well to moderate (hepatocyte-like)
Main aetiology
HBV
Alcohol, HCV, NASH
Genetic features
Chromosomal instability
Chromosomal stability
FGF19/CCND1 amplification
Chromosome 7 amplification
17p loss
TERT promoter mutation


Genetic features
TERT promoter mutation
TP53 mutation
CTNNB1 mutation
AXIN1 mutation
TSC1–TSC2 mutation
RPS6KA3 mutation
Main signalling pathways
Cell cycle, mTOR, RAS–MAPK, MET signalling
IGF1R
PKA
Wnt–TGFβ signalling
AKT signalling
Cell cycle proliferation
Progenitor features: IGF2, AFP, EPCAM+
IL6–JAK–STAT signalling
++
+
Wnt–β-catenin signalling
Epigenetic features
Global DNA hypomethylation
Extensive promoter hypermethylation (CDKN2A, CDH1)
36 CpG signature
miRNA class C
miRNA class B
miRNA class A
Immunological features
Immune-active
Immune-exhausted
Immune-active
Immune-excluded
High immune infiltrate (↑ M2 macrophages)
High immune infiltrate (↑ T cells)
Low immune infiltrate
Prognosis
More aggressive tumours
Less aggressive tumours
Vascular invasion
High frequency
Low frequency
Serum AFP
High levels
Low levels

HCC clinical

Clinical Features at Presentation

Symptoms	Percent of Patients
None	23%
Abdominal	
Ascites	8%
Jaundice	8%
Anorexia/weight loss	10%
Malaise	6%
Bleeding	4%
Encephalopathy	2%

HCC- Diagnosis

Diagnosis is made by non-invasive methods

Sonography, TC and/or RM

A bioptic confirmation is needed in selected cases (<5%)

Usually the tumor is detected during fullow up programs in high risk populations

(i.e. cirrhotic patients of any etiology)

Diagnosis

- Diagnosis generally relies on pathology
- **Non-invasive criteria can be used in patients with cirrhosis**
  - Peculiar vascular derangement occurs during hepatic carcinogenesis
  - High pre-test probability of HCC

Recommendations
Diagnosis of **HCC in cirrhotic** patients should be based on **non-invasive criteria and/or pathology**
In **non-cirrhotic** patients, diagnosis of HCC should be confirmed by **pathology**
Pathological diagnosis of HCC should be **based on International Consensus recommendations**[1,2] using the required histological and immunohistological analyses

1. International Consensus Group for Hepatocellular Neoplasia. Hepatology 2009;49:658–64;
2. Bosman FT, et al. WHO Classification of Tumours of the Digestive System. Fourth Edition. IARC press; 2010;
EASL CPG HCC. J Hepatol 2018; doi: 10.1016/j.jhep.2018.03.019

Non-invasive diagnosis

- Non-invasive diagnostic criteria for patients with cirrhosis require particular imaging techniques

Recommendations
Non-invasive criteria* can **only be applied to cirrhotic patients** for nodule(s) ≥1 cm, in light of the high pre-test probability, and are based on imaging techniques obtained by **multiphasic CT, dynamic contrast-enhanced MRI**…
…or CEUS
Because of their **higher sensitivity** and the analysis of the whole liver, **CT** or **MRI** should be used **first**
FDG PET scan is not recommended for early diagnosis of HCC because of the **high false-negative rate**

*Diagnosis is based on the identification of the typical hallmarks of HCC, which differ according to imaging techniques or contrast agents (APHE with washout in the portal venous or delayed phases on CT and MRI using extracellular contrast agents or gadobenate dimeglumine, APHE with washout in the portal venous phase on MRI using gadoxetic acid, APHE with late-onset [>60 seconds] washout of mild intensity on CEUS)

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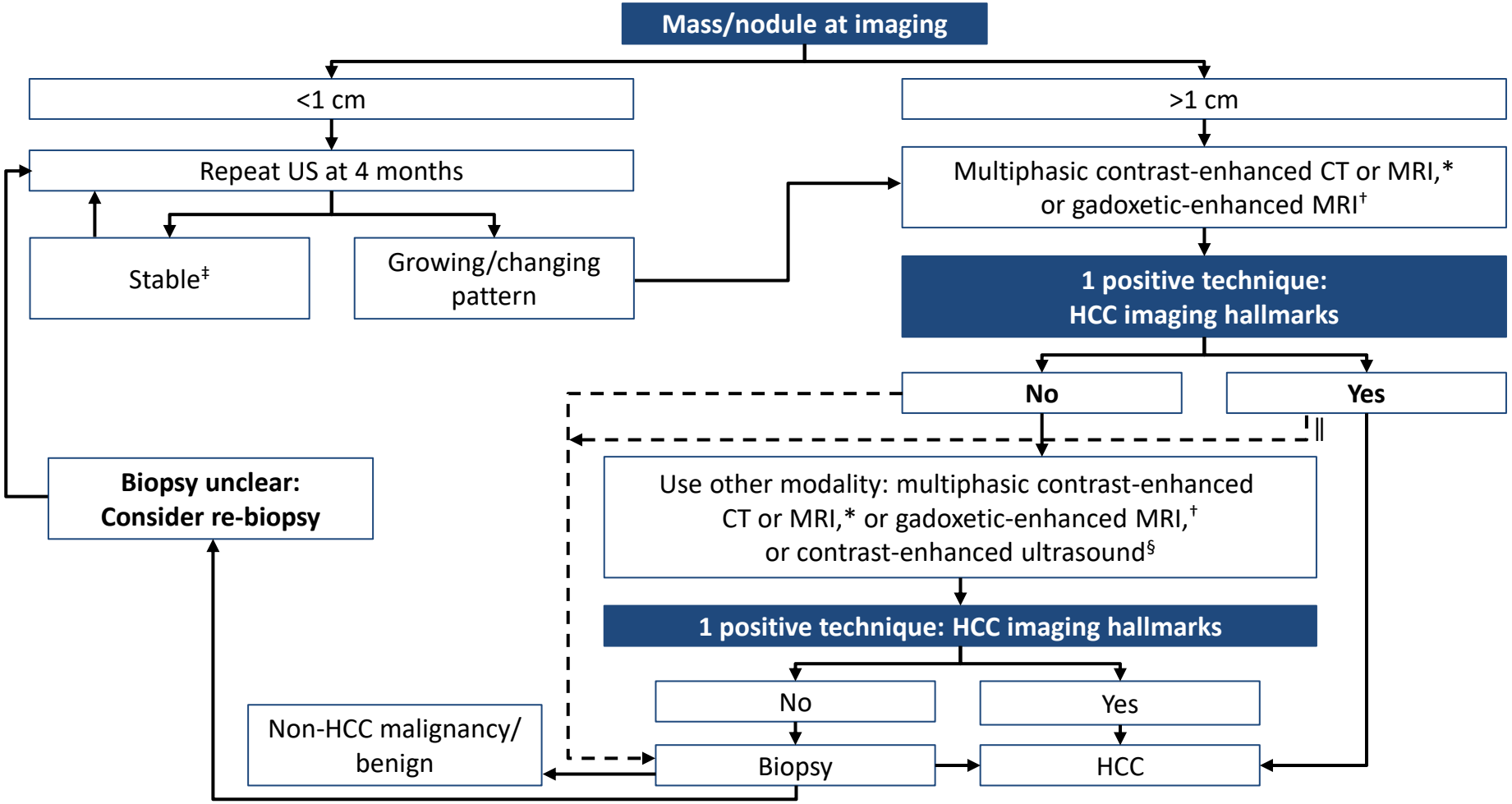
Algorithm for diagnosis and recall in cirrhotic liver



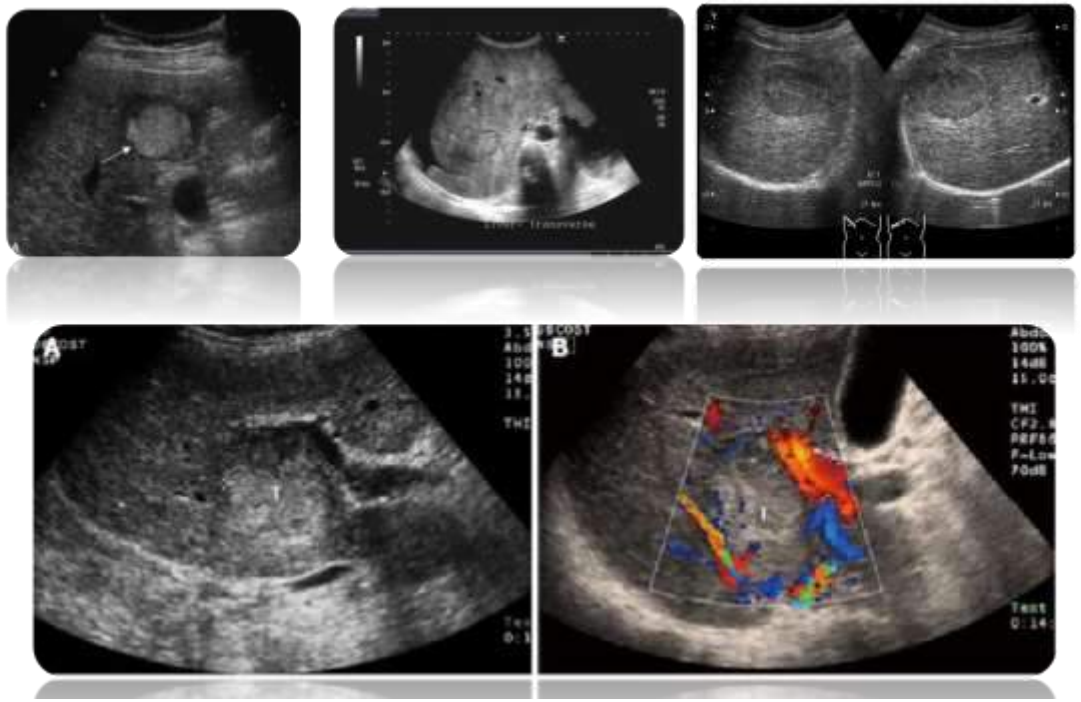
*Using extracellular MRI contrast agents or gadobenate dimeglumine; †Diagnostic criteria: APHE and washout on the portal venous phase; ‡Lesion <1 cm stable for 12 months (three controls after 4 months) can be shifted back to regular 6-month surveillance; §Diagnostic criteria: APHE and mild washout after 60 seconds; ‖Optional for centre-based programmes

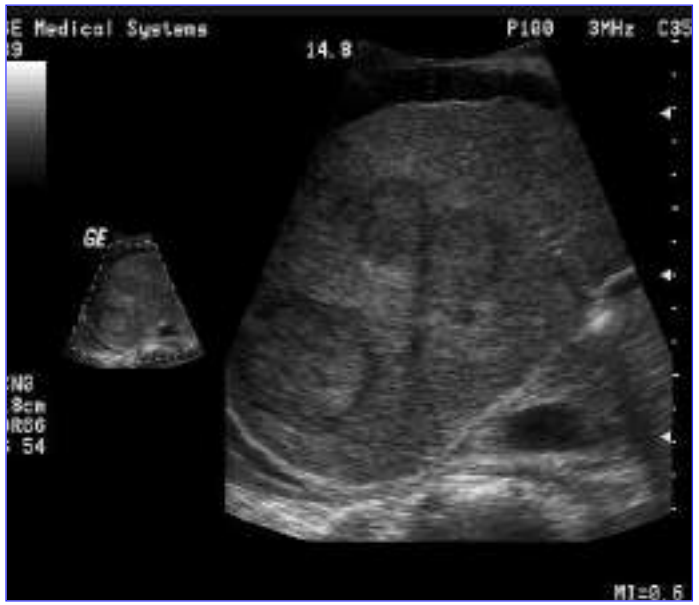
EASL CPG HCC. J Hepatol 2018; doi: 10.1016/j.jhep.2018.03.019

HCC- Staging

Table 1 BCLC stage of HCC

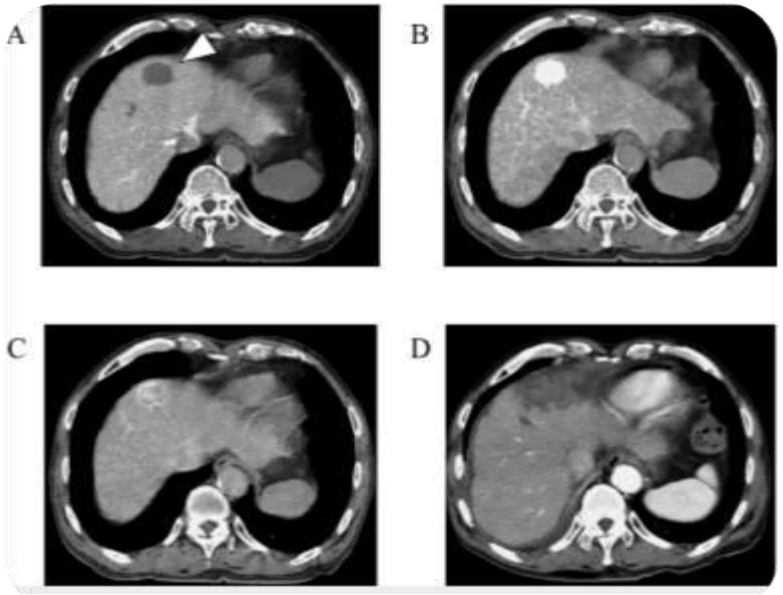
Stage	PS score	Tumor		Liver function
		Tumor number	Tumor size	
Very early stage (Stage 0)	0	Single tumor	<2 cm	Without portal hypertension
Early stage (Stage A)	0	Single tumor	Any	Child-Pugh A-B
		Less than 3	<3 cm	Child-Pugh A-B
Intermediate stage (Stage B)	0	Multinodular tumor	Any	Child-Pugh A-B
Advance stage (Stage C)	1-2	Portal invasion or N1, M1	Any	Child-Pugh A-B
End stage (Stage D)	3-4	Any	Any	Child-Pugh C

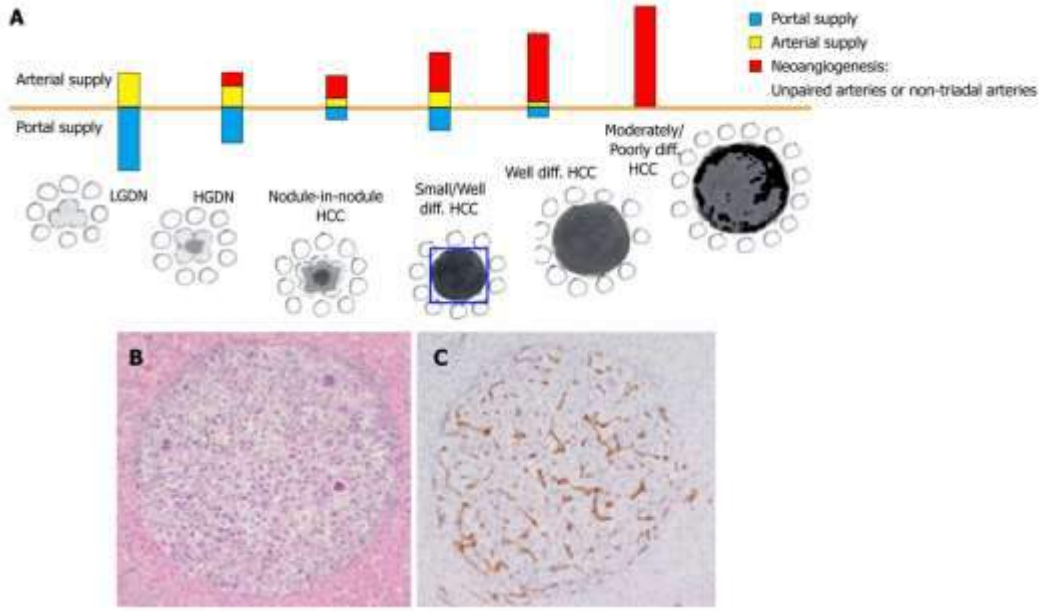


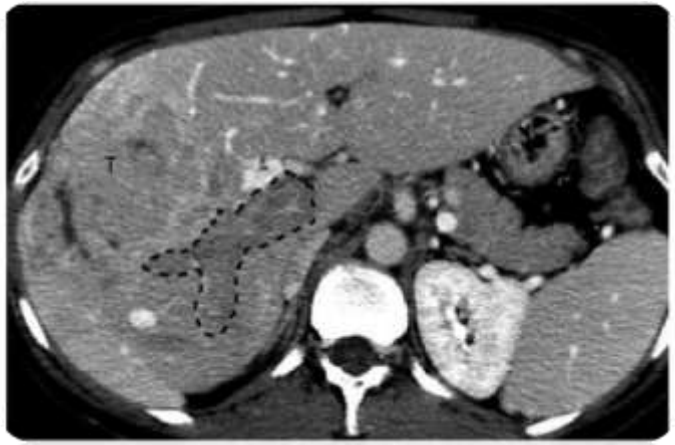


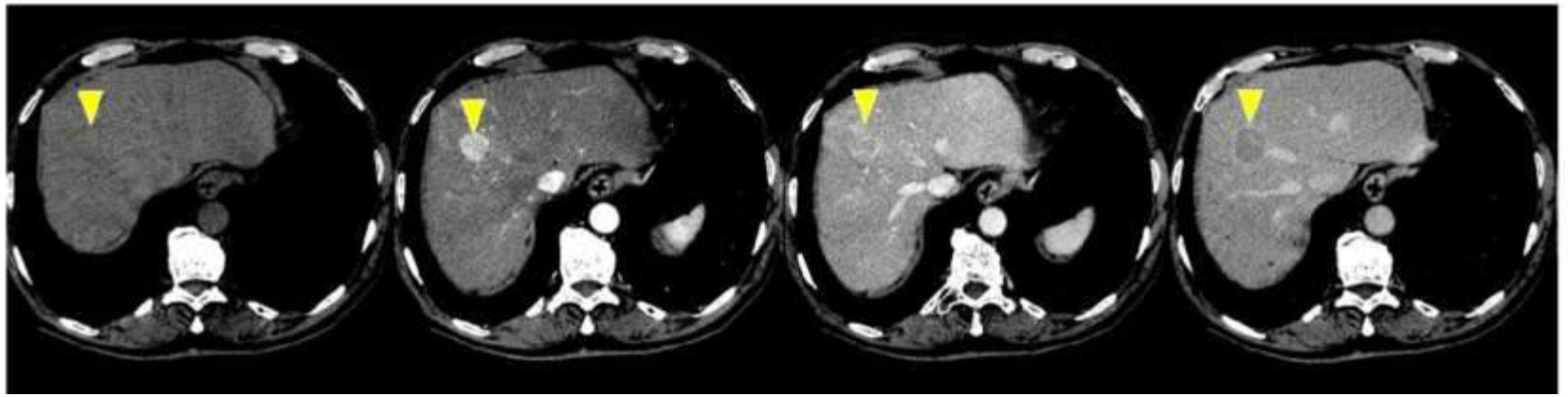
Fiorucci S. Atlante di ecografia in gastroenterologia ed epatologia. Vol I-II-Pacini Ed. 2003

HCC- Staging

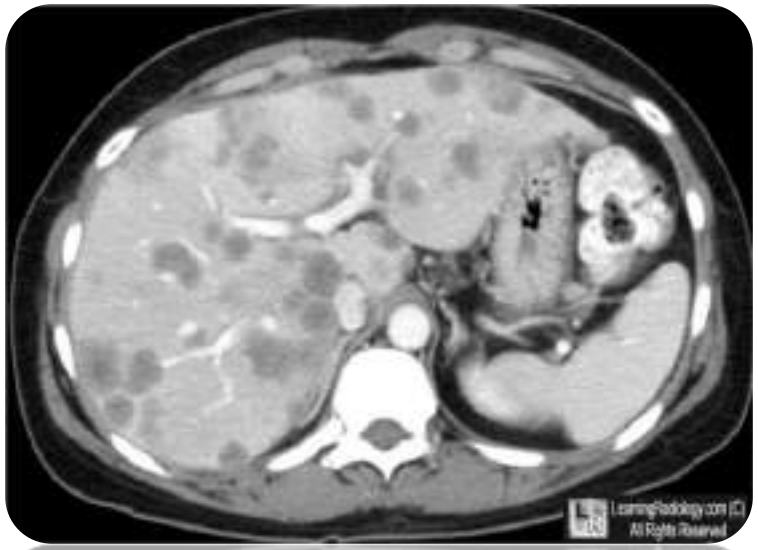

A
B
C
D

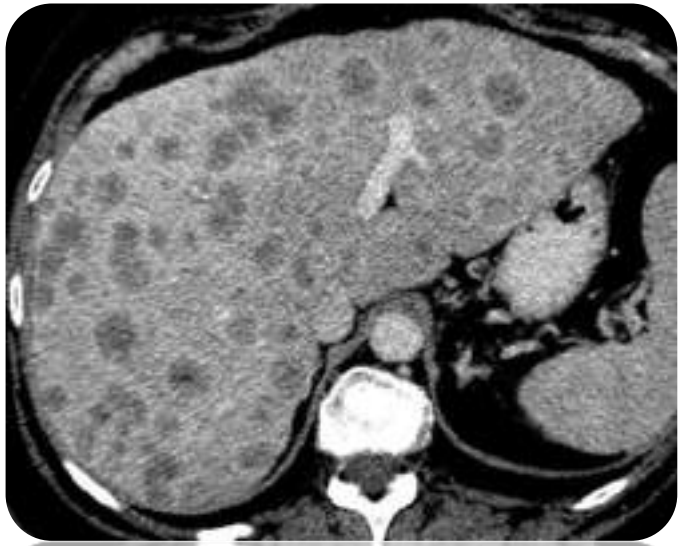

A
Arterial supply
Portal supply
LGDN
HGDN
Nodule-in-nodule HCC
Small/Well diff. HCC
Well diff. HCC
Moderately/ Poorly diff. HCC
Portal supply
Arterial supply
Neoangiogenesis:
Unpaired arteries or non-triadal arteries
B
C

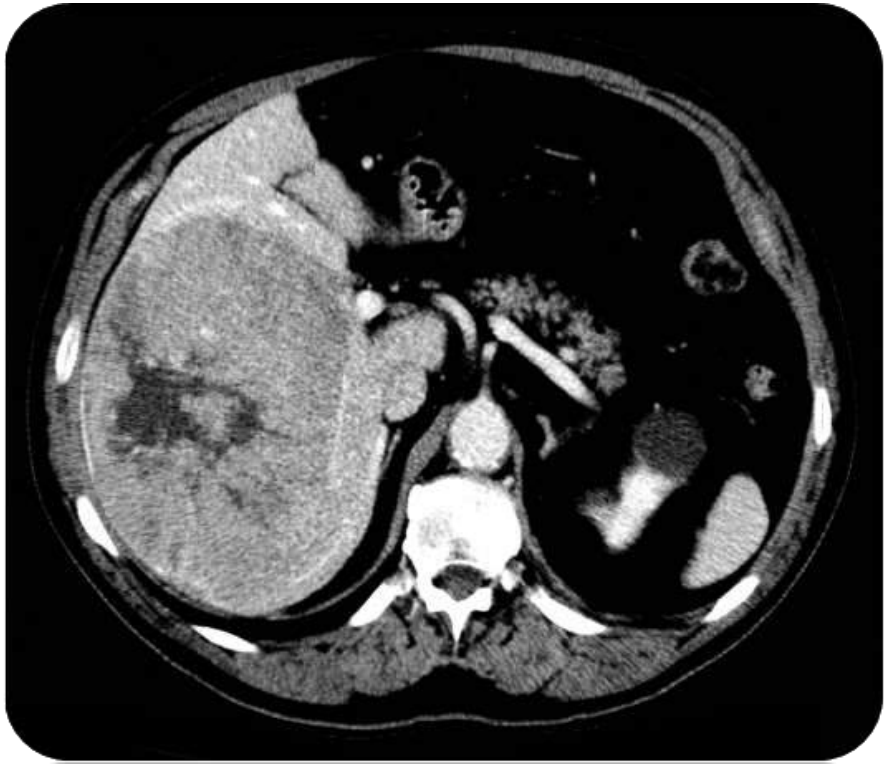




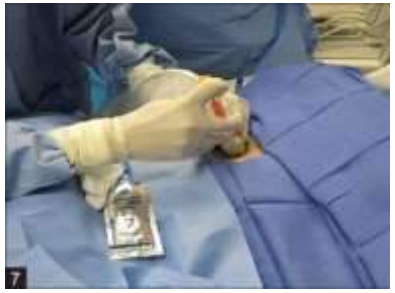
HCC- diagnosis

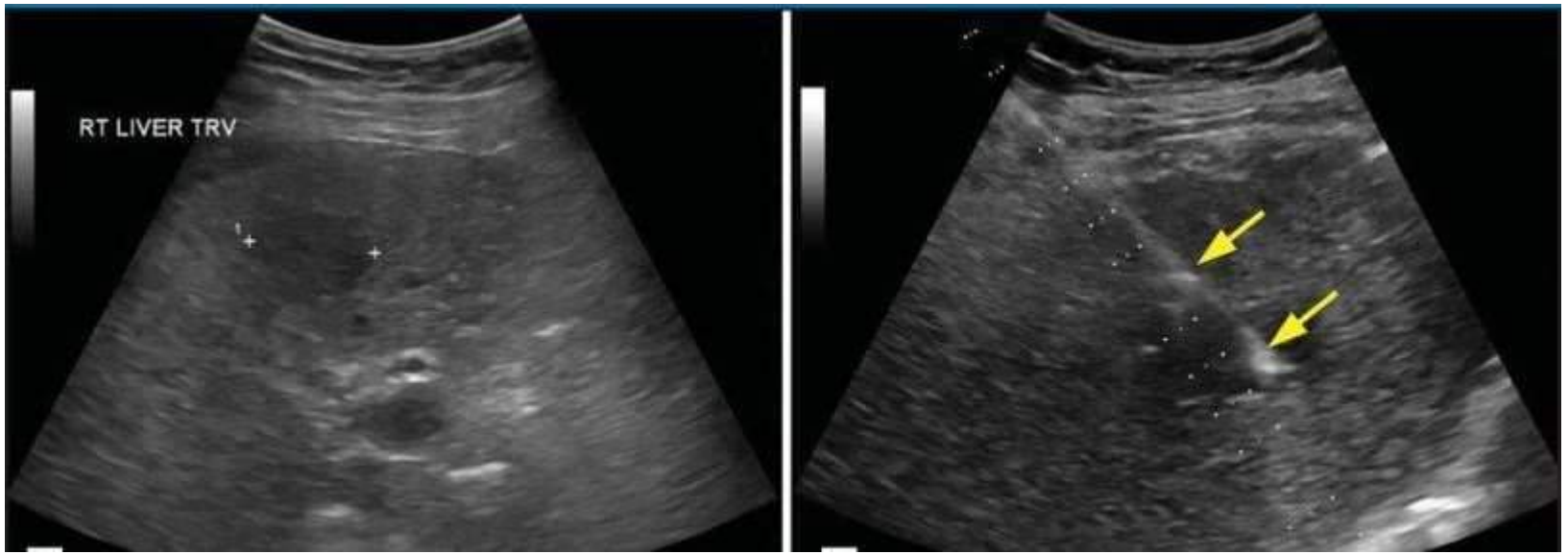


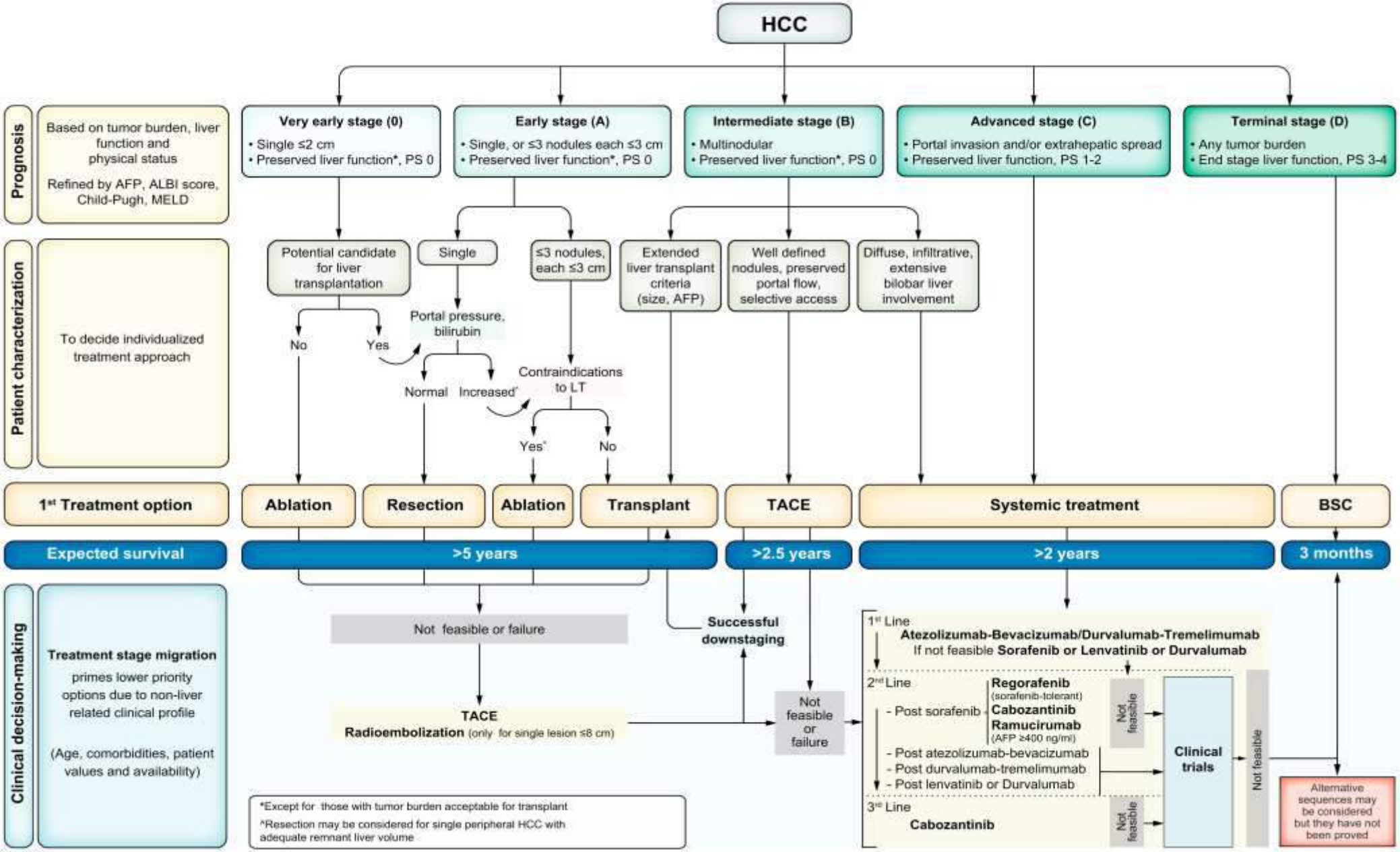




HCC-liver biopsy







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Treatment of HCC: liver resection

- Surgery is the mainstay of HCC treatment
  - Best outcomes of any treatment in well-selected candidates
    - 5-year survival of 60–80%
- **Liver resection** and **transplantation** is first option with early tumours
  - Extended to other stages after non-surgical tumour downstaging

Recommendations		
Surgical resection is the treatment of choice in patients with **HCC** arising on a **non-cirrhotic** liver	Low	Strong
Indications for resection of HCC in cirrhosis should be based on: • Multi-parametric composite assessment of liver function • Portal hypertension • Extent of hepatectomy and expected volume of future liver remnant • Performance status • Patient co-morbidities	High	Strong
Peri-resection mortality in **cirrhotic patients** should be **<3%**	High	Strong

EASL CPG HCC. J Hepatol 2018; doi: 10.1016/j.jhep.2018.03.019

Liver resection and tumour parameters

- Indications and choice of surgical technique depend on tumour size and location(s)

Recommendations	Level of evidence	Grade of recommendation
Liver resection is recommended for single HCC of any size **In particular**, for tumours **>2 cm** when **hepatic function** is **preserved** and sufficient **remnant liver volume** is **maintained**	Moderate	Strong
In properly trained centres, **liver resection should be considered via laparoscopic/minimally invasive approaches**, especially for tumours in anterolateral and superficial locations	Moderate	Weak
HCC presenting with two or three **nodules within Milan criteria may be eligible for liver resection depending on:** • Performance status • Co-morbidities • Preservation of liver function and remnant volume	Low	Weak

EASL CPG HCC. J Hepatol 2018; doi: 10.1016/j.jhep.2018.03.019

Treatment of HCC: liver transplantation

- Together with NAFLD/NASH, HCC is the fastest growing indication for LT
- Milan criteria are the benchmark for selecting patients for LT
  - Basis for comparison with other suggested criteria

Recommendations	Level of evidence	Grade of recommendation
LT is recommended as the **first-line option** for HCC **within Milan criteria** but **unsuitable for resection**	High	Strong
Consensus on expanded criteria for LT in HCC has not been reached • Patients outside Milan criteria can be considered for LT after successful downstaging to within Milan criteria, within defined protocols	Moderate	Weak
Composite criteria,* are **likely** to **replace conventional criteria** for defining transplant feasibility	Low	Strong
Tumour vascular invasion and extrahepatic metastases are an **absolute contraindication** for LT in HCC	High	

*That consider surrogates of tumour biology and response to neoadjuvant treatments to bridge or downstage tumours in combination with tumour size and number of nodules: these criteria should be investigated and determined *a priori*, validated prospectively and auditable at any time

EASL CPG HCC. J Hepatol 2018; doi: 10.1016/j.jhep.2018.03.019

Liver transplant prioritization

- Prioritization of cadaveric graft allocation is challenging

Recommendations	Level of evidence	Grade of recommendation
The use of **marginal cadaveric grafts** for LT in patients with HCC has **no contraindication**	Moderate	
Prioritizing a cadaveric graft allocation, for patients with or without HCC, within a common waiting list, is complex: • **No system can serve all regions** • Prioritization **criteria** for HCC **should at least include:** – Tumour burden – Tumour biology indicators – Waiting time – Response to tumour treatment	Moderate	Strong
Transplant **benefit** may need to be considered **alongside** the conventional transplant principles of **urgency** and **utility** in decision making, depending on list composition and dynamics	Moderate	Weak

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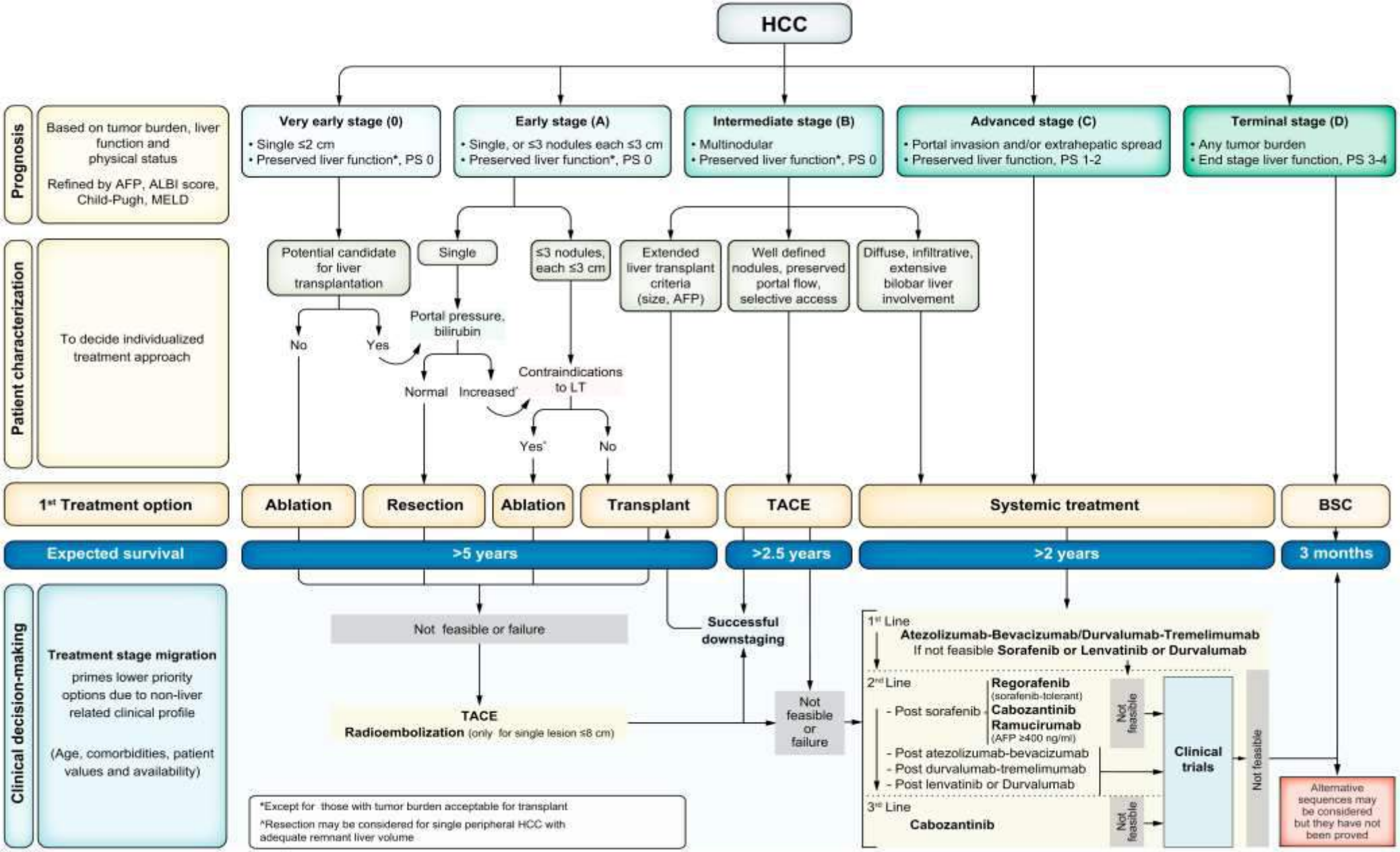

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Local ablation and external radiation

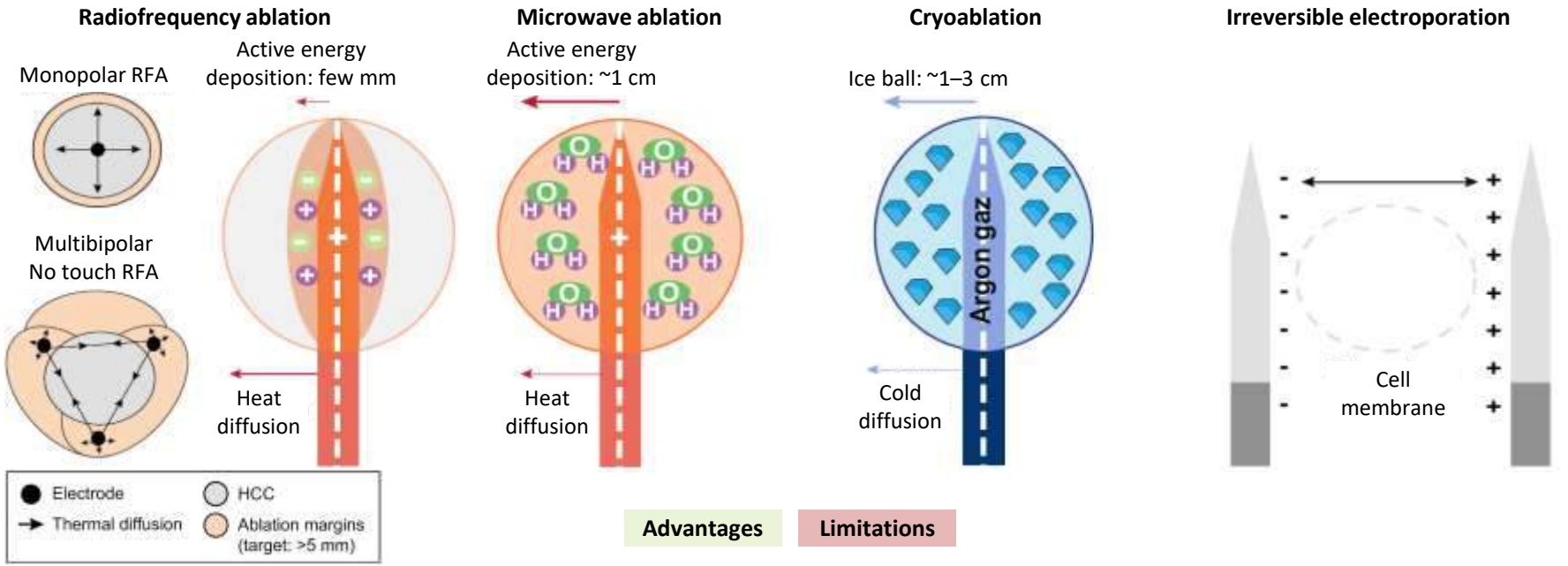
- Tumour ablation techniques have improved along with the imaging-guidance tools required to ensure their successful application

Recommendations	Level of evidence	Grade of recommendation
Thermal ablation with **radiofrequency** is the **standard of care** for patients with BCLC-0 and A tumours **not suitable for surgery***	High	Strong
In patients with **very early stage HCC** (BCLC-0) **radiofrequency ablation** in **favourable locations** can be adopted as **first-line therapy** even in **surgical patients**	Moderate	Strong
Microwave ablation showed promising results for local control and survival	Low	
Ethanol injection is an option in some cases **where thermal ablation** is **not technically feasible**, especially in tumours <2 cm	High	Strong
External beam radiotherapy is under investigation • So far there is no robust evidence to support this therapeutic approach in the management of HCC	Low	Weak

*Thermal ablation in single tumours 2–3 cm in size is an alternative to surgical resection based on technical factors (location of the tumour), hepatic and extrahepatic patient conditions

EASL CPG HCC. J Hepatol 2018; doi: 10.1016/j.jhep.2018.03.019

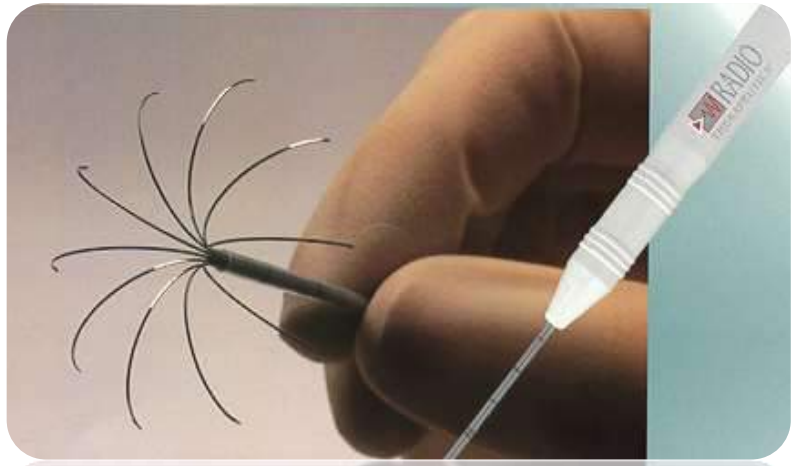
Percutaneous ablation

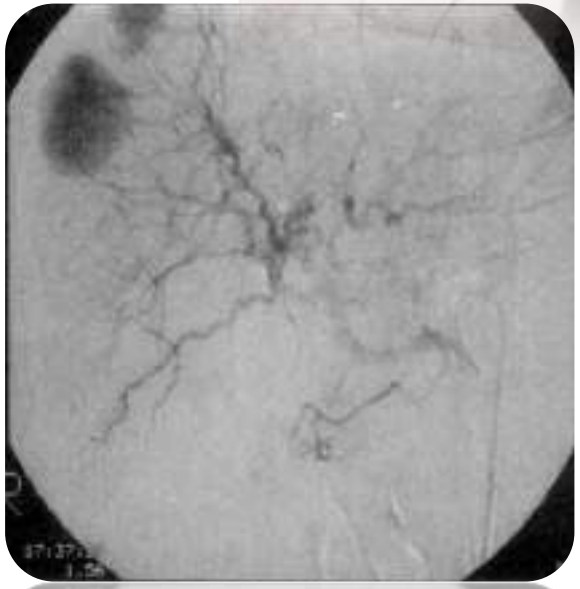


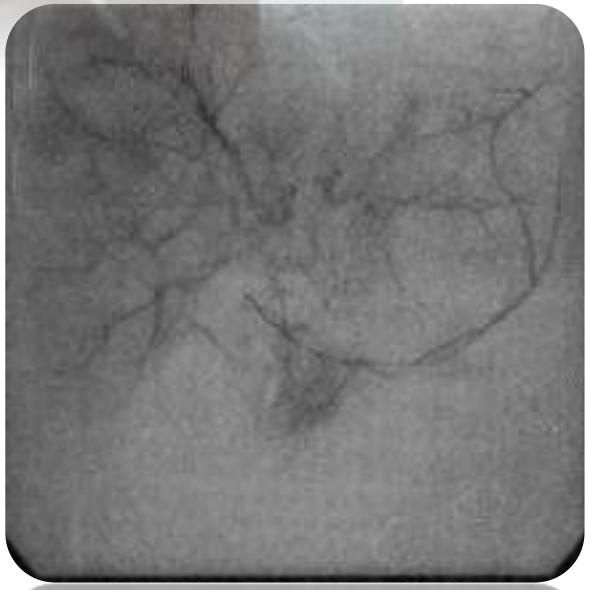
	Advantages	Limitations	
• Well-evaluated treatment (reference) • Multibipolar mode: increases volume and predictability (margin) of ablation zone	• Higher and faster temperature picks reached than with RFA (less sensitive to heat sink effect than monopolar RFA)	• Easy monitoring with imaging of ice ball progression	• Limited risk of thermal injury to neighbouring critical structures • Unsensitive to heat sink effect • Advantage of multibipolar mode (no touch technique, predictability of margins)
• Thermal injury of adjacent structure • Heat sink effect (near major vessels) • Multibipolar mode is less sensitive to heat sink effect	• No reliable endpoint to set the amount of energy deposition	• Cryoshock with first device • Limited clinical data available with new devices	• Only preliminary clinical data • General anaesthesia using curare and major analgesic drugs is mandatory

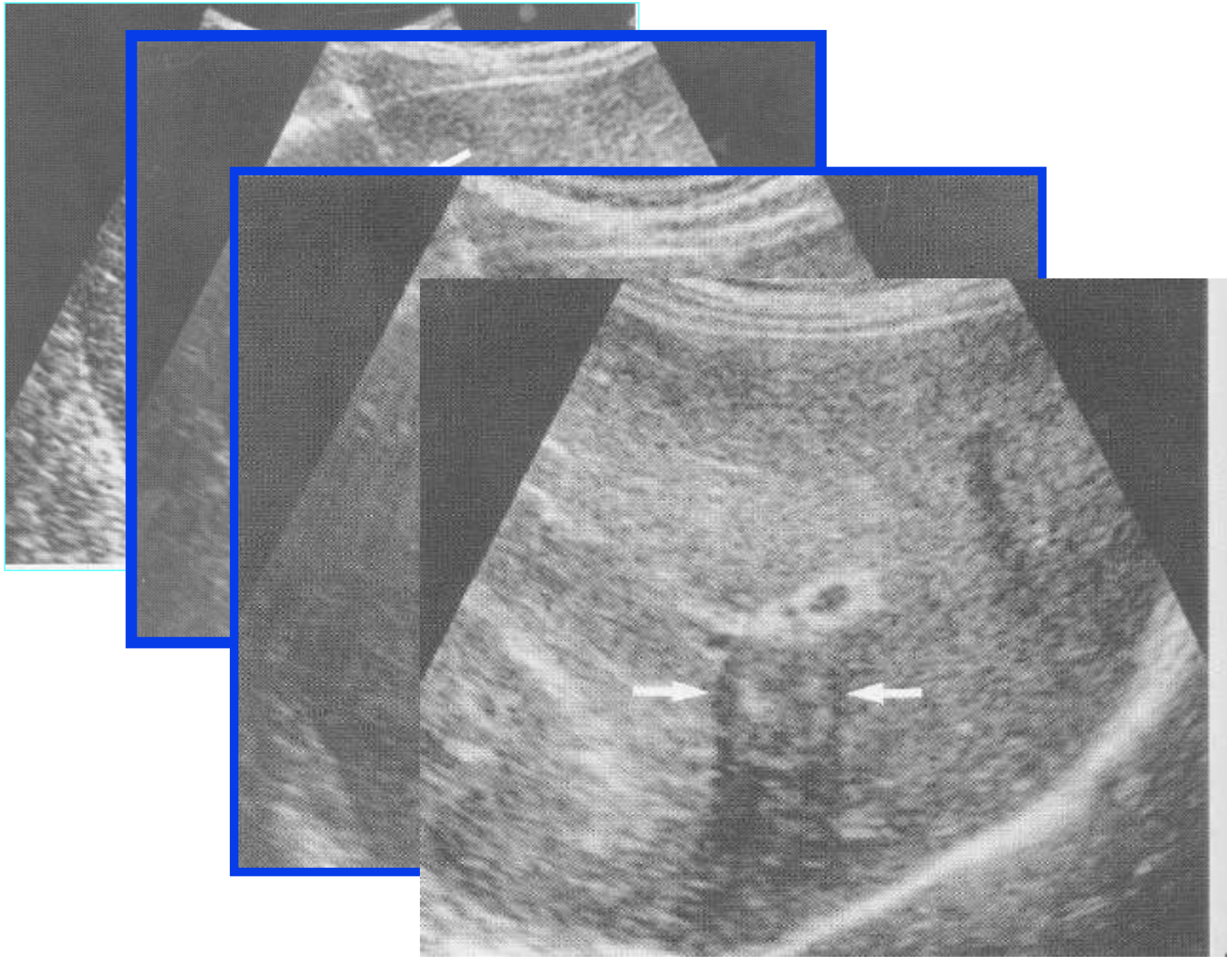
Nault J-C, et al. J Hepatol 2018;68:783–97
EASL CPG HCC. J Hepatol 2018; doi: 10.1016/j.jhep.2018.03.019

Radiofrequency Ablation

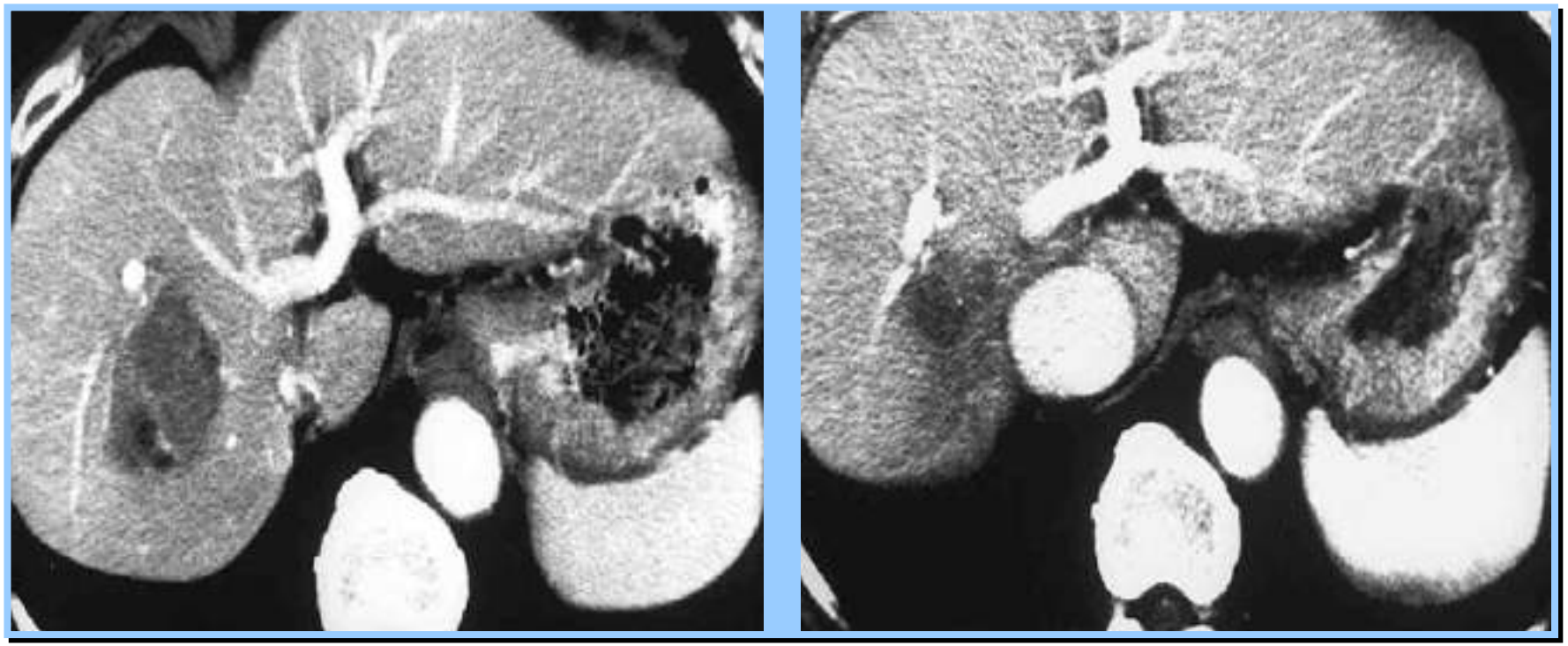


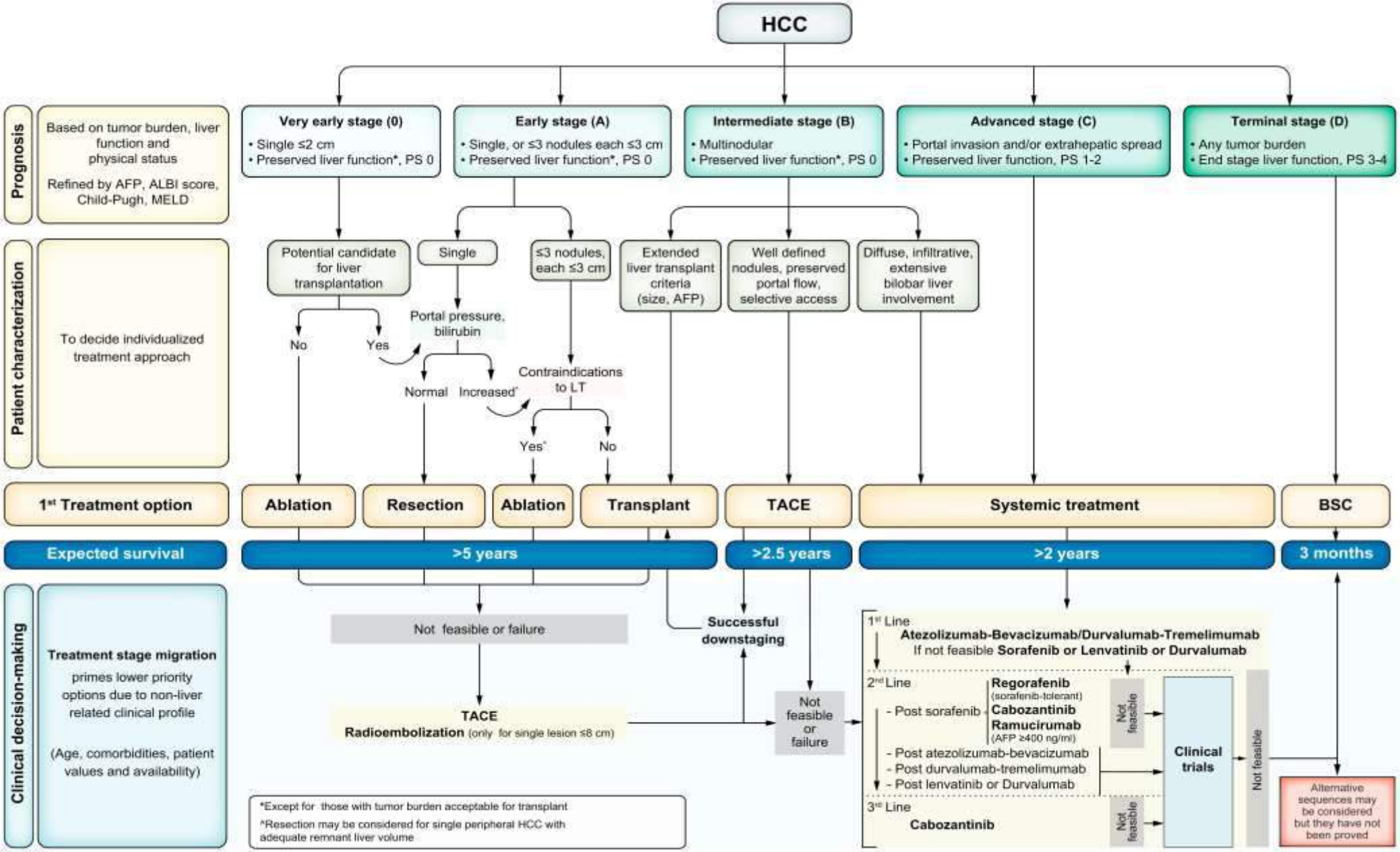




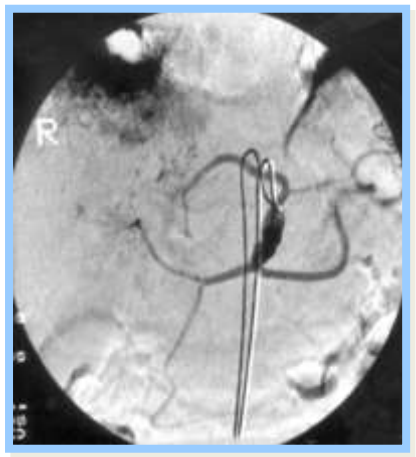


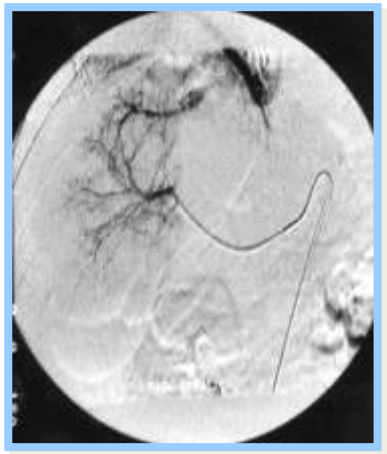
Radiofrequency ablation

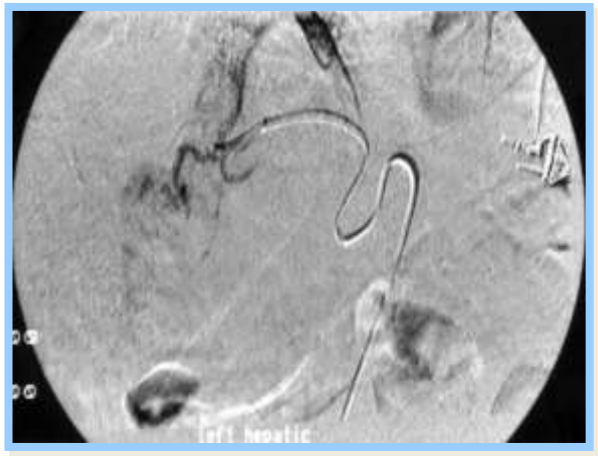


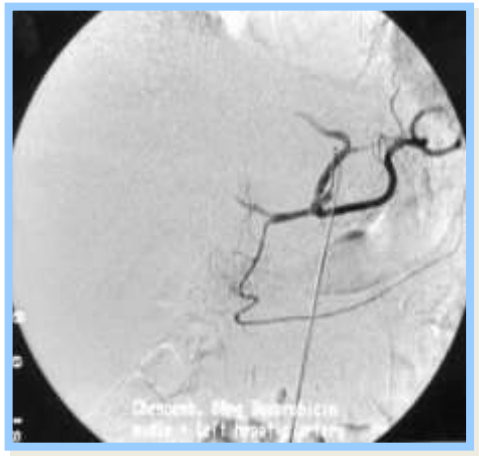

HCC
Prognosis
Based on tumor burden, liver function and physical status
Refined by AFP, ALBI score, Child-Pugh, MELD
Very early stage (0)
• Single ≤2 cm
• Preserved liver function*, PS 0
Early stage (A)
• Single, or ≤3 nodules each ≤3 cm
• Preserved liver function*, PS 0
Intermediate stage (B)
• Multinodular
• Preserved liver function*, PS 0
Advanced stage (C)
• Portal invasion and/or extrahepatic spread
• Preserved liver function, PS 1-2
Terminal stage (D)
• Any tumor burden
• End stage liver function, PS 3-4
Patient characterization
To decide individualized treatment approach
Potential candidate for liver transplantation
Single
≤3 nodules, each ≤3 cm
Extended liver transplant criteria (size, AFP)
Well defined nodules, preserved portal flow, selective access
Diffuse, infiltrative, extensive bilobar liver involvement
No
Yes
Portal pressure, bilirubin
Normal
Increased^
Contraindications to LT
Yes^
No
1st Treatment option
Ablation
Resection
Ablation
Transplant
TACE
Systemic treatment
BSC
Expected survival
>5 years
>2.5 years
>2 years
3 months
Clinical decision-making
Treatment stage migration
primes lower priority options due to non-liver related clinical profile
(Age, comorbidities, patient values and availability)
Not feasible or failure
Successful downstaging
TACE
Radioembolization (only for single lesion ≤8 cm)
Not feasible or failure
1st Line
Atezolizumab-Bevacizumab/Durvalumab-Tremelimumab
If not feasible Sorafenib or Lenvatinib or Durvalumab
2nd Line
- Post sorafenib
Regorafenib (sorafenib-tolerant)
Cabozantinib
Ramucirumab (AFP ≥400 ng/ml)
- Post atezolizumab-bevacizumab
- Post durvalumab-tremelimumab
- Post lenvatinib or Durvalumab
3rd Line
Cabozantinib
Not feasible
Clinical trials
Not feasible
Alternative sequences may be considered but they have not been proved
*Except for those with tumor burden acceptable for transplant
^Resection may be considered for single peripheral HCC with adequate remnant liver volume

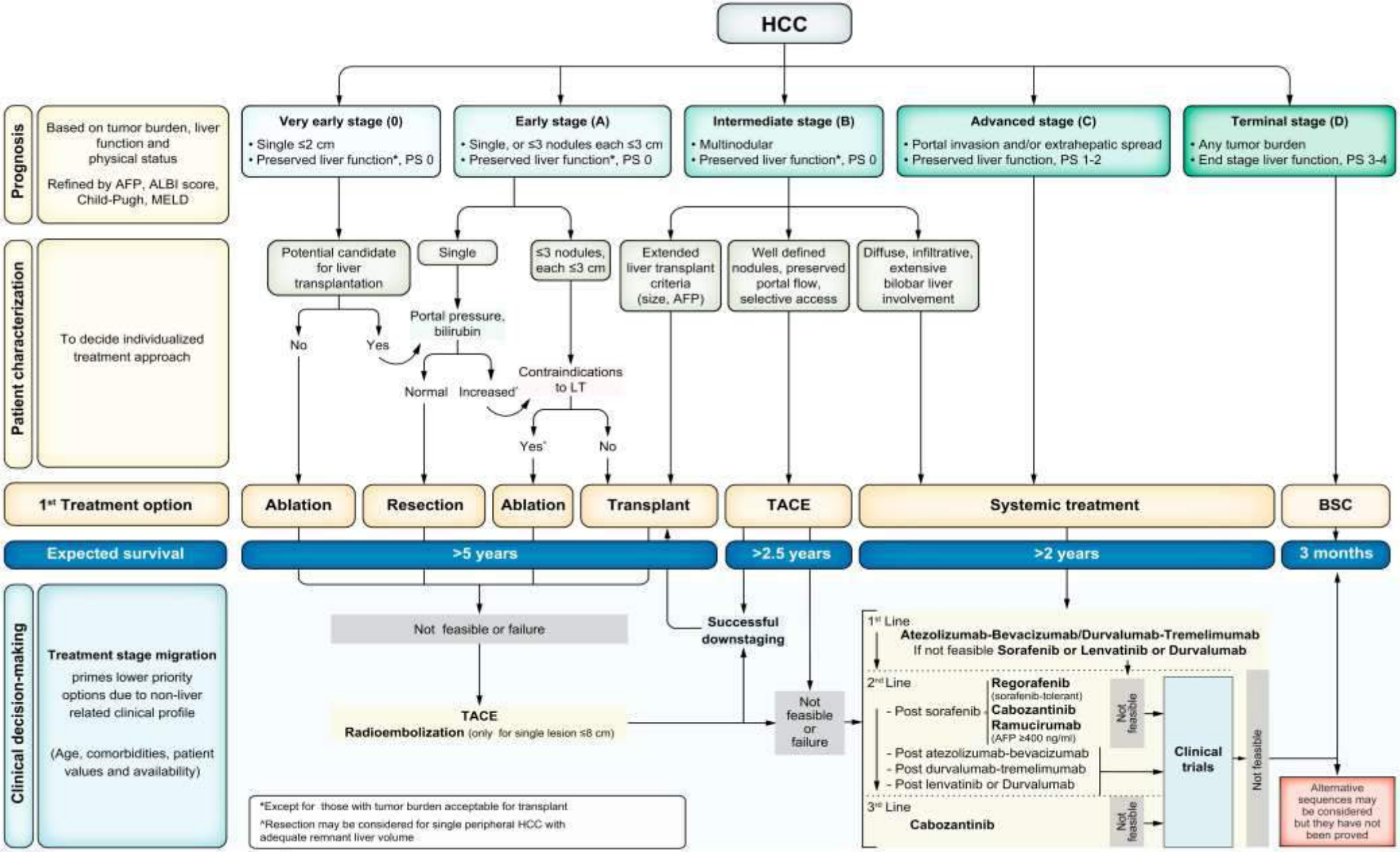
Trans-arterial Chemoembolization for Hepatocellular Cancer











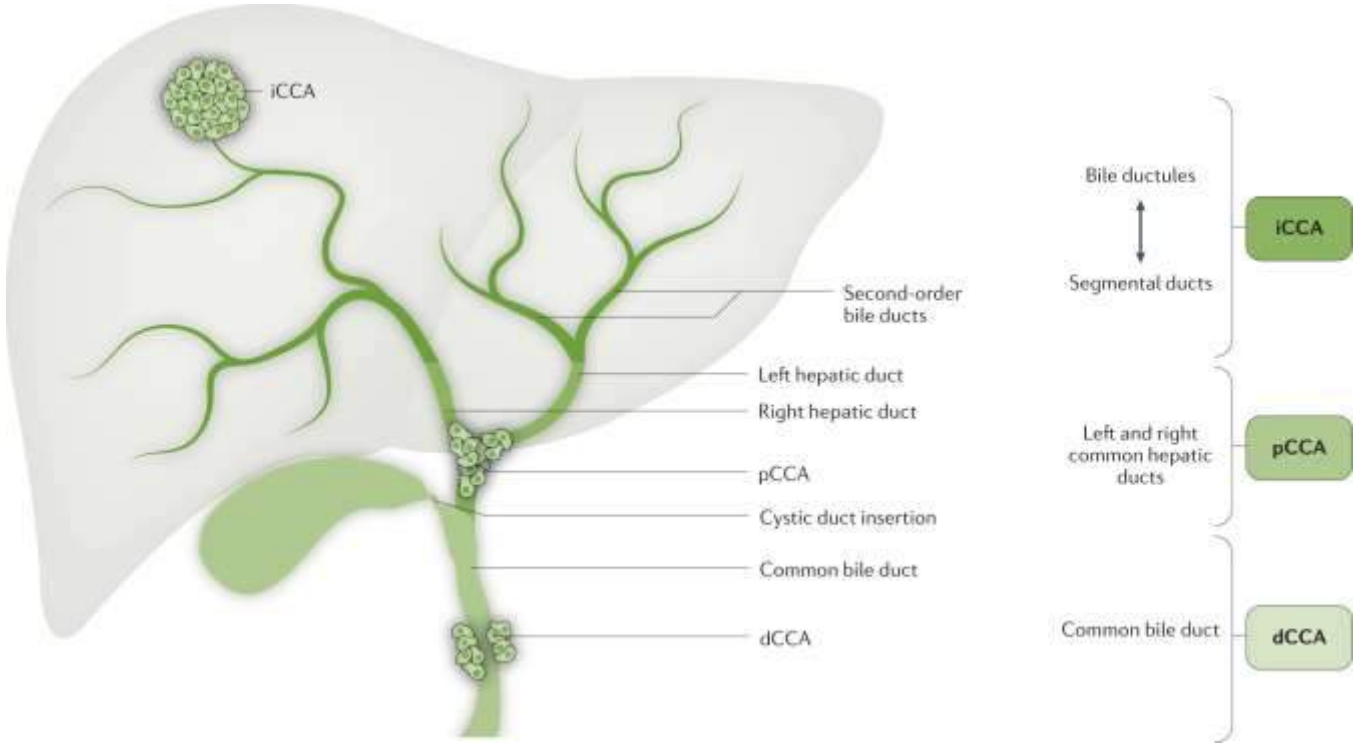
Journal of Hepatology 2022 76681-693DOI: (10.1016/j.jhep.2021.11.018)

Biliary tract cancers

Classification of biliary tract cancers

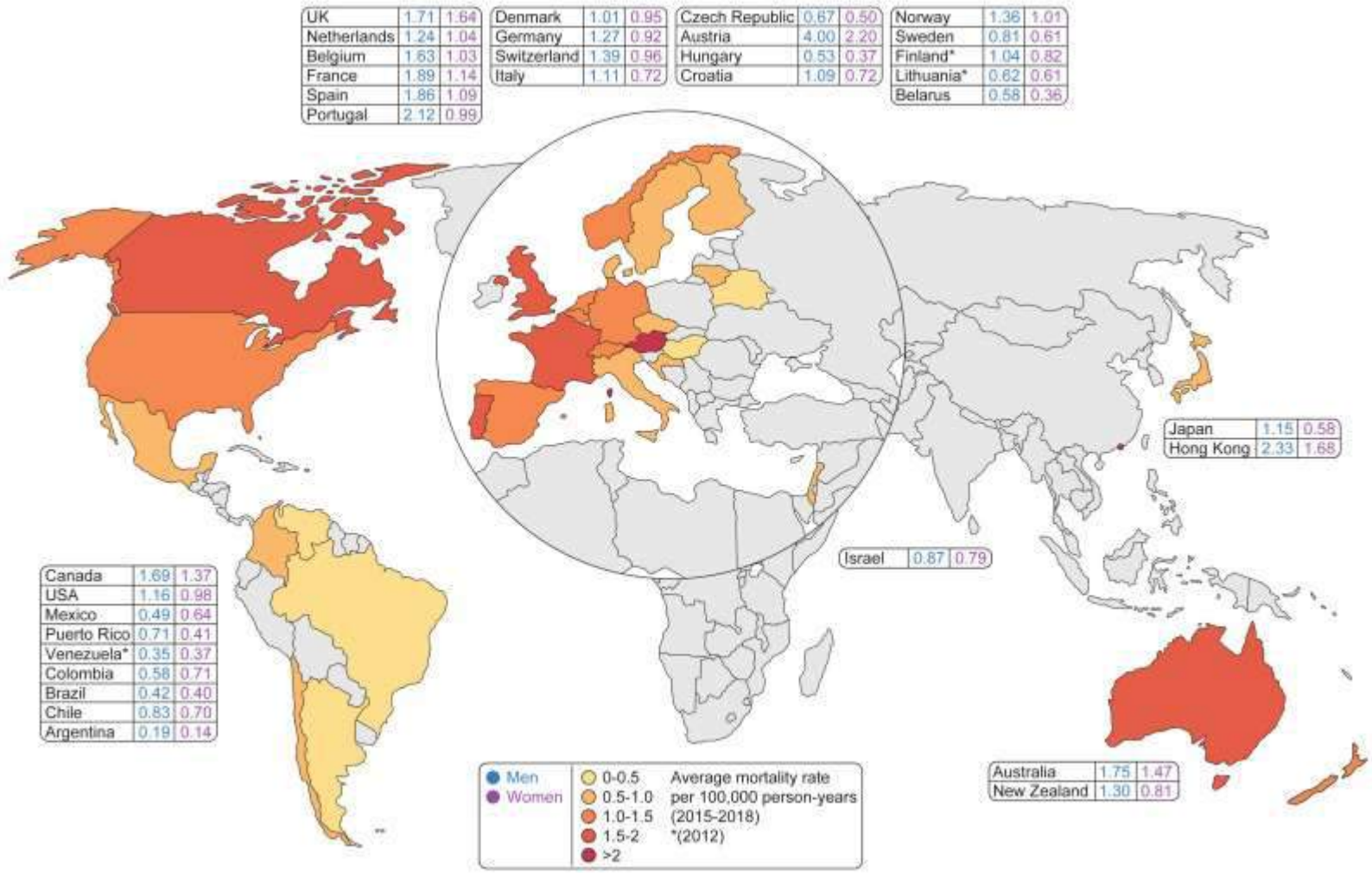
Current anatomic classification of CCA considers

iCCA as the subtype arising between the bile ductules and the second-order bile ducts (i.e. segmental bile ducts),
pCCA as the subtype arising in the right and/or left hepatic duct and/or at their junction and
dCCA as the subtype involving the common bile duct.

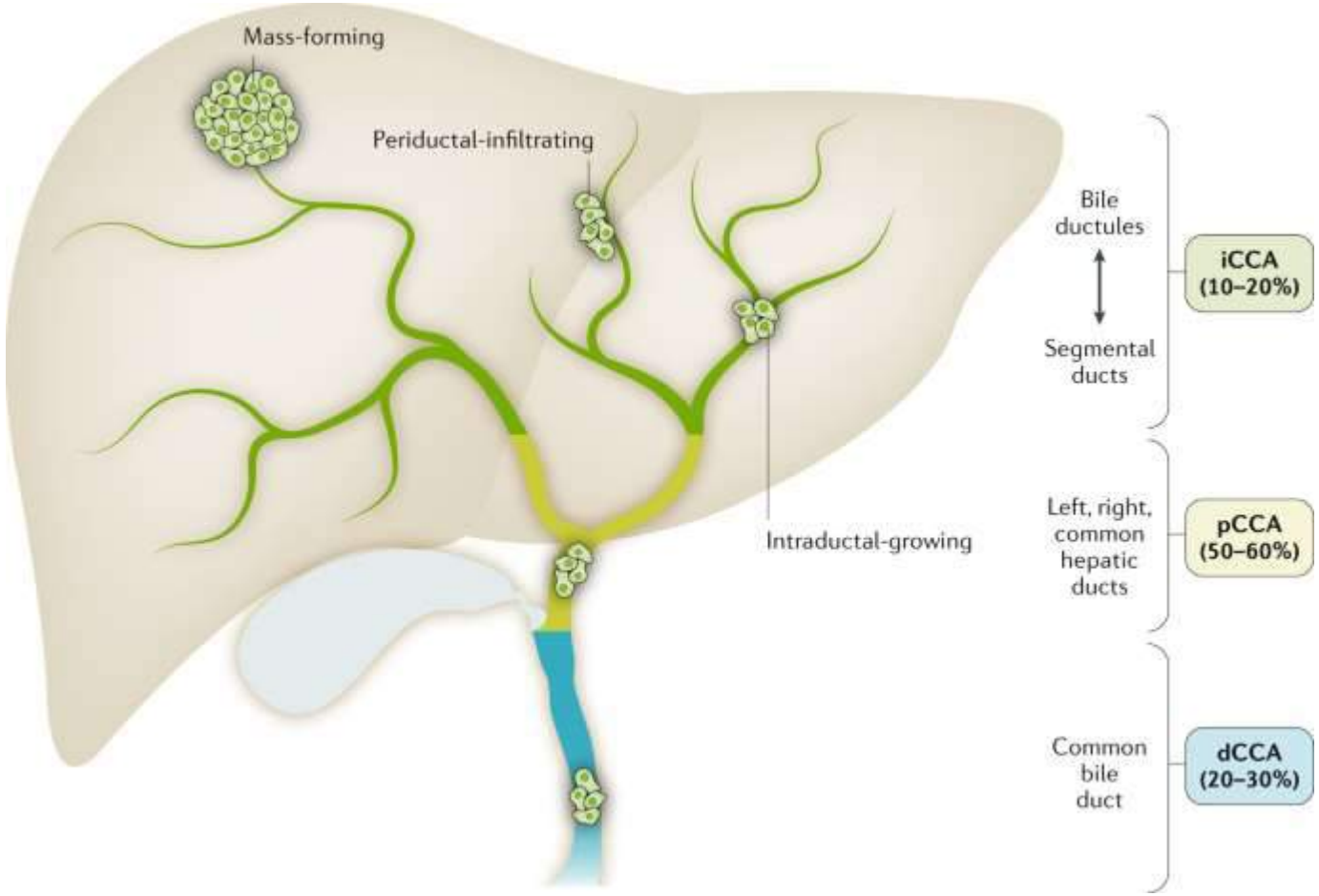


Cholangiocarcinoma (CCA) is best classified according to the primary, anatomic subtype as intrahepatic CCA (iCCA), perihilar CCA (pCCA) and distal CCA (dCCA). iCCA is located proximally to the second-order bile ducts within the liver parenchyma. pCCA is localized between the second-order bile ducts and the insertion of the cystic duct into the common bile duct. dCCA is confined to the common bile duct below the cystic duct insertion.
Brindley, P.J., Bachini, M., Ilyas, S.I. *et al.* Cholangiocarcinoma. *Nat Rev Dis Primers* **7,** 65 (2021). https://doi.org/10.1038/s41572-021-00300-2

Cholangiocarcinoma



Anatomical classification of proximal and distal CCA (Klatskin Tumor)



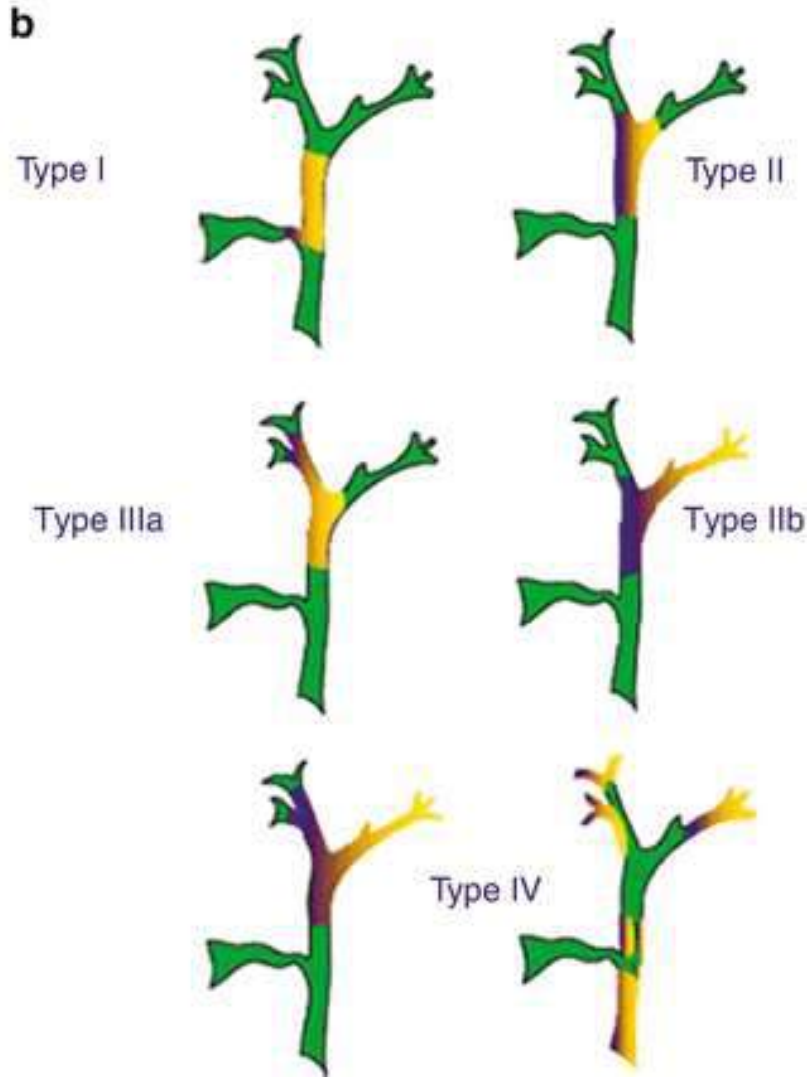
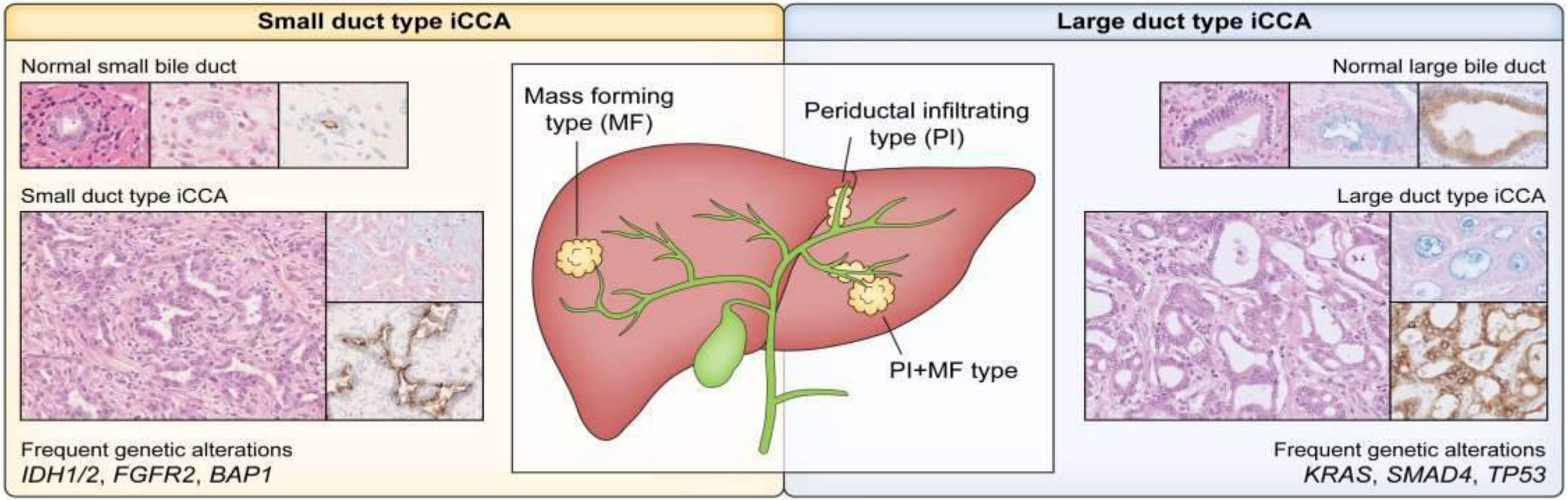


Fig. 2



Macroscopically, iCCA is categorised **into four subtypes**: mass-forming (MF; iCCA with nodular aspect), periductal-infiltrating (PI; iCCA infiltrating along the bile duct), MF+PI (i.e. iCCA infiltrating along the bile duct with concurrent invasion into neighbouring liver parenchyma, causing a mass), and intraductal growing

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Table 3. Risk factors for iCCA.

Risk factors for iCCA	Study type	OR/RR
Liver diseases		
Choledochal cyst	Meta-analysis	OR 26.71
Choledocholithiasis	Meta-analysis	OR 10.08
Cholelithiasis	Meta-analysis	OR 3.38
Cholecystolithiasis	Meta-analysis	OR 1.75
Caroli disease	Population-based study	OR 38
Primary sclerosing cholangitis	Population-based study	OR 22
Cirrhosis	Meta-analysis	OR 15.32
Chronic hepatitis B	Meta-analysis	OR 4.57
Chronic hepatitis C	Meta-analysis	OR 4.28
Haemochromatosis	Population-based study	OR 2.1
Non-alcoholic fatty liver disease	Meta-analysis	OR 2.2
Extrahepatic comorbidities		
Inflammatory bowel disease	Meta-analysis	OR 2.68
Chronic pancreatitis	Population-based study	OR 2.7
Type 2 diabetes mellitus	Meta-analysis	OR 1.73
Obesity	Meta-analysis	OR 1.14
Hypertension	Meta-analysis	OR 1.10
Parasitic infections		
Liver fluke (*Opisthorchis viverrini*, *Clonorchis sinensis*)	Meta-analysis	OR 5 iCCA > eCCA
Lifestyle habits		
Alcohol consumption	Meta-analysis	OR 3.15
Cigarette smoking	Meta-analysis	OR 1.25
Environmental toxins		
Thorotrast (until 1969)	Retrospective study	RR >300
1,2- Dichloropropane	Retrospective study	RR 15
Asbestos	Case-control study	OR 4.8
Asbestos	Case-control study	OR 1.1–1.7

eCCA, extrahepatic cholangiocarcinoma; iCCA, intrahepatic cholangiocarcinoma; OR, odds ratio; RR, relative risk.
Adapted and updated from Banales JM *et al.*[249]

Pathogenesis and management of CCA subtypes

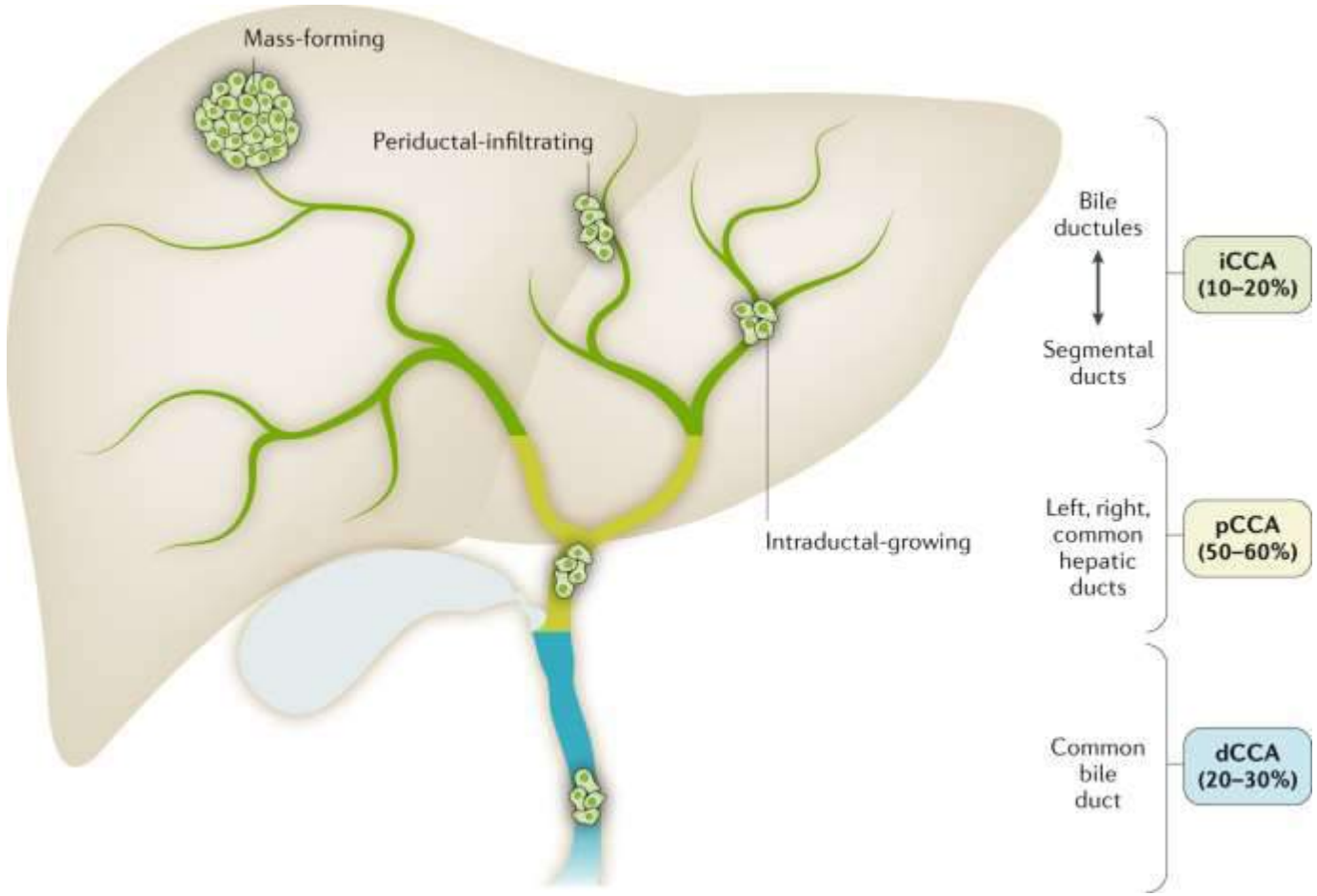
CCA, cholangiocarcinoma; dCCA, distal CCA; ERC, endoscopic retrograde cholangiography; iCCA, intrahepatic CCA; MRCP, magnetic resonance cholangiopancreatography; pCCA, perihilar CCA.

Table 2 | **Clinicopathological and molecular features of cholangiocarcinoma**

CCA type	Gross pattern	Precancerous lesion	Underlying disease	Tissue markers[a]	Frequent mutations
iCCA—CLC	Mass-forming	None	Viral, cirrhosis	NCAM	*IDH1/2*, *FGFR2* fusions, *BAP1*, *BRAF*, *ARID1A*, *KRAS*, *TP53*, *SMAD4* Increased *IDH1* and *TP53*
iCCA—small duct type	Mass-forming	None	Viral, cirrhosis	NCAM, N-cadherin, SMAD4, BAP1^{loss}	*IDH1/2*, *FGFR2* fusions, *BAP1*, *BRAF*, *ARID1A*, *KRAS*, *TP53*, *SMAD4* Increased *IDH1/2*, *FGFR2* fusion
iCCA—large duct type	Periductal infiltrating (±mass-forming) or intraductal growing	Biliary epithelial neoplasia, IPNB, ITPN, mucinous cystic neoplasm	Primary sclerosing cholangitis, liver flukes	Mucin[b], MUC5AC, MUC6, S100P, SMAD4^{loss}, BAP1	*IDH1/2*, *FGFR2* fusions, *BAP1*, *BRAF*, *ARID1A*, *KRAS*, *TP53*, *SMAD4* Increased *KRAS* and *TP53*
pCCA–dCCA	Periductal infiltrating or intraductal growing	Biliary epithelial neoplasia, IPNB, ITPN, mucinous cystic neoplasm	Primary sclerosing cholangitis, liver flukes	Mucin[b], MUC5AC, MUC6, S100P, SMAD4^{loss}, BAP1	*KRAS*, *TP53*, *SMAD4*, *ERBB3*, *PRKACA–PRKACB* fusions, *ELF3*

CCA, cholangiocarcinoma; CLC, cholangiolocarcinoma; dCCA, distal cholangiocarcinoma; iCCA, intrahepatic cholangiocarcinoma; IPNB, intraductal papillary neoplasm of the bile duct; ITPN, intraductal tubulopapillary neoplasm; pCCA, perihilar cholangiocarcinoma. [a]Markers from single-centre experience; international criteria and consensus on a definite panel of markers are still needed. [b]Mucin

CCA



Bilirubin total > conjugated (direct)

γGT

ALP

GOT/GPT

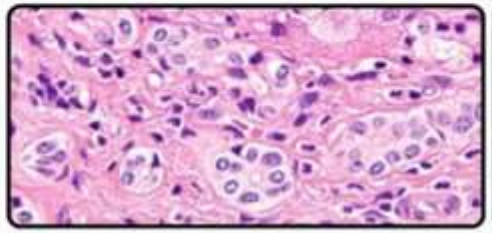
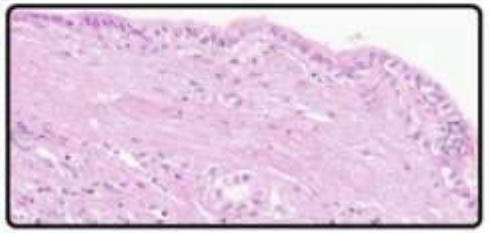
Cholesterol and triglycerides

iCCA

Pruritus

Jandice

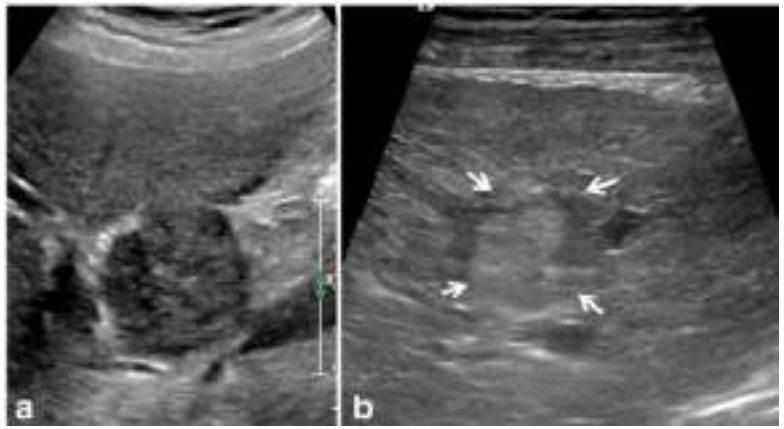
Fever and pain in the right upper quadrant

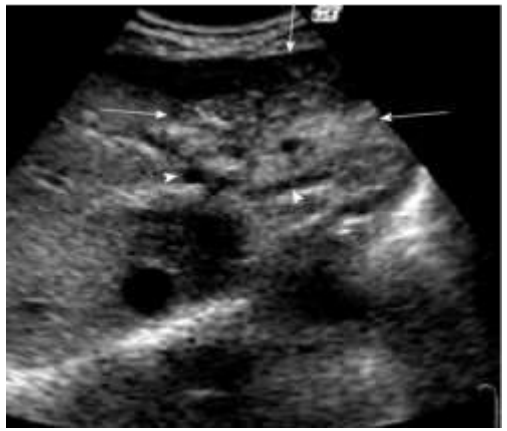
Intrahepatic Cholangiocarcinoma		
Classification	Small Duct Type	Large Duct Type
Gross Type	Mass-forming	Mixed / Periductal Infiltrating
Cell of Origin		
	Canal of Hering Bile ductule	Columnar cholangiocytes Peribiliary glands
Main Etiology	Chronic hepatitis HBV / HCV Alcoholic / Metabolic	Hepatolithiasis Liver fluke PSC
Immuno-histochemistry & Mucin stain	NCAM N-cadherin CRP	S100P Mucin
Frequent Mutations	*BAP1* *IDH1/2* *FGFR2 fusion*	*KRAS* *TP53* *SMAD4*
Suggested Molecular Classification*	Inflammation Class	Proliferation Class
Patient Outcome	Favorable	Poor

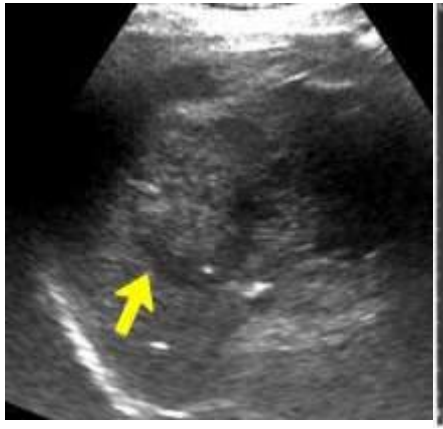
iCCA diagnosis

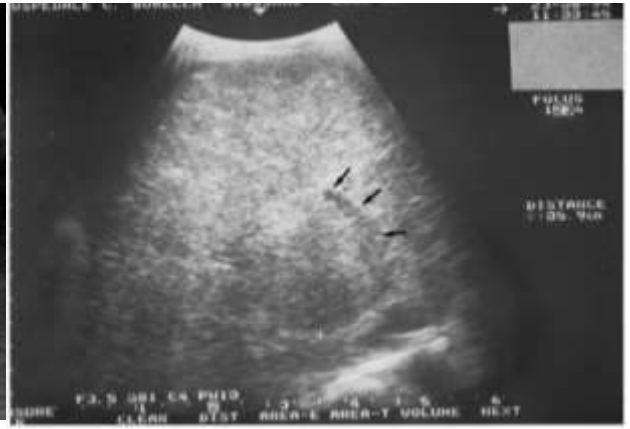
Usually, the first suspicion of iCCA is raised on ultrasound, where iCCA appears as a solid mass with aspecific variable echogenicity (mixed, hypo, or hyperechogenic) with possible dilatation of bile ducts peripheral to the mass.

The benefit of contrast-enhanced ultrasound in iCCA is controversial,









iCCA diagnosis

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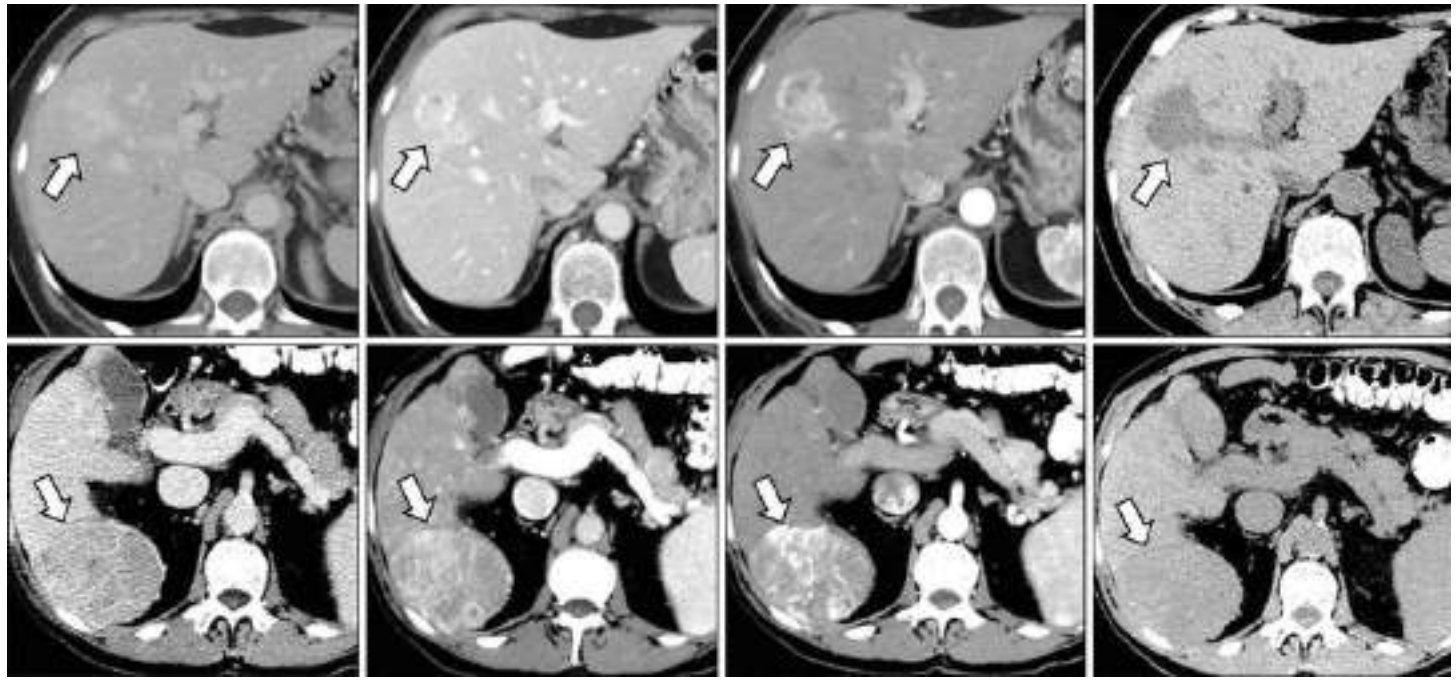
The benefit of contrast-enhanced ultrasound in iCCA is controversial,

At CT, with an unenhanced scan, iCCA appears hypodense with respect to surrounding parenchyma, shows irregular borders and, in some cases, capsular retraction may be observed.

At contrast-enhanced scans, the most frequent behaviour is peripheral rim enhancement in the arterial phase (“targetoid” appearance) followed by delayed progression of peripheral to central enhancement caused by tumour fibrosis.

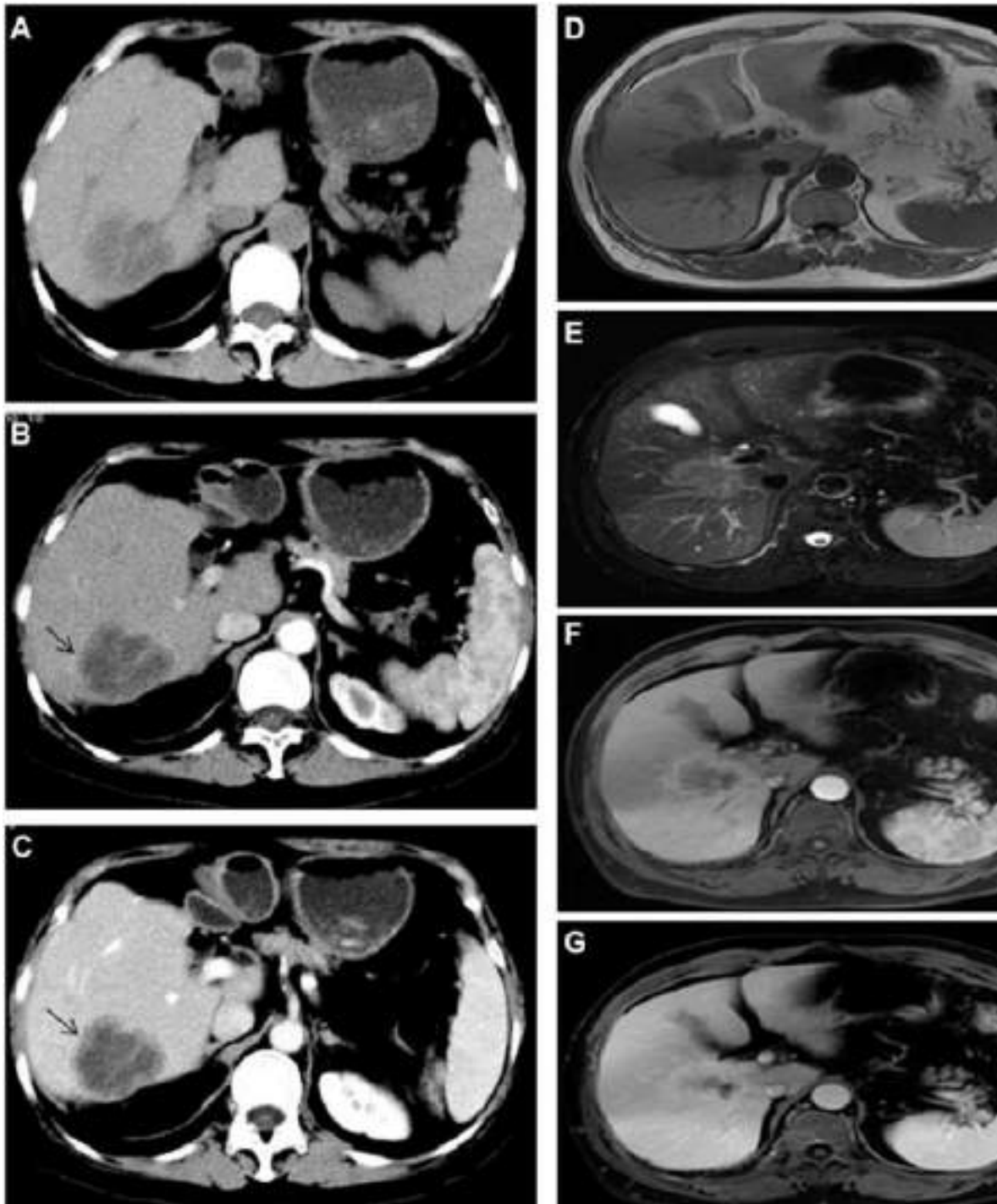
However, arterial enhancement is seen in some small MF-iCCAs, mimicking HCC.

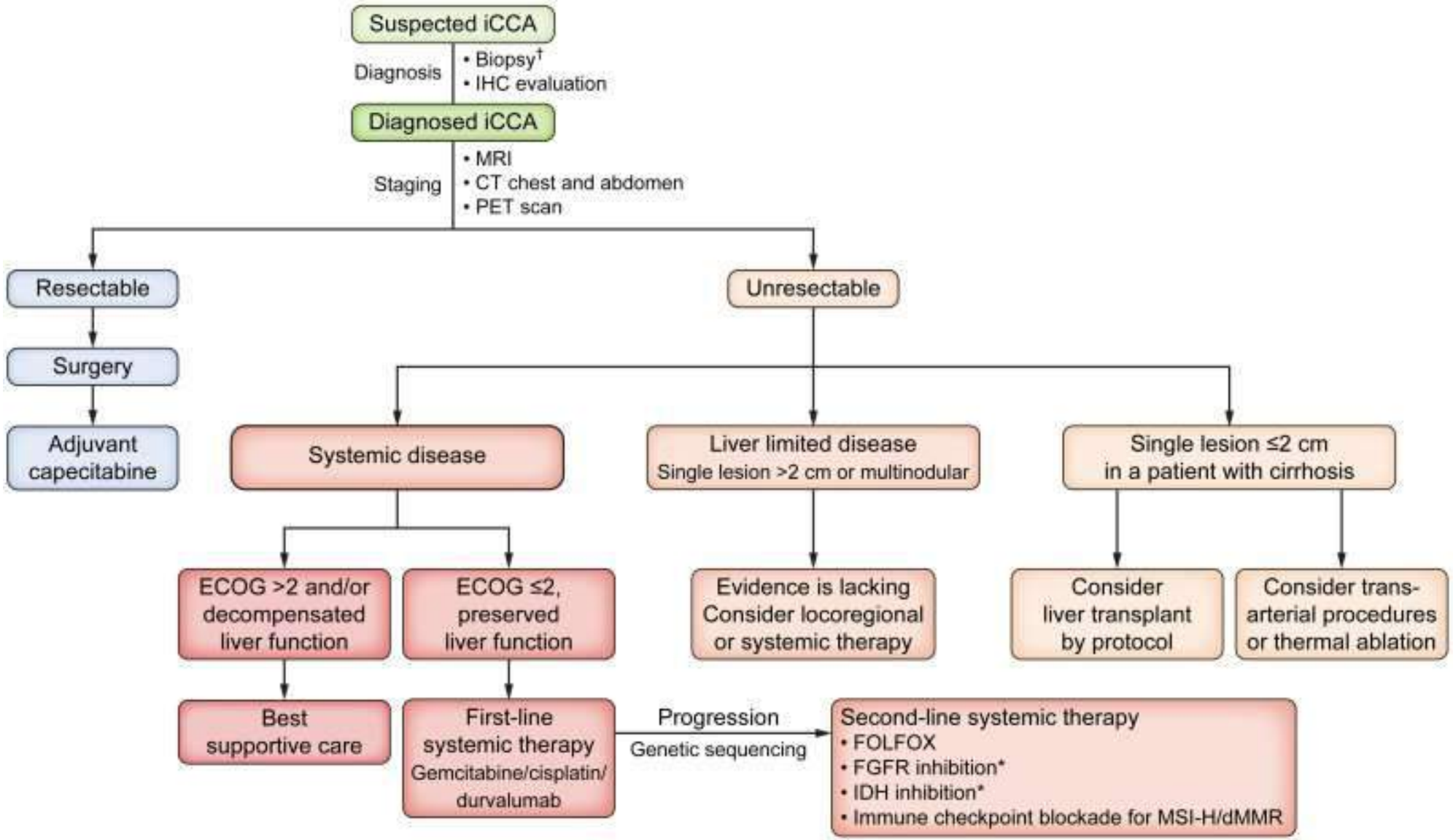


iCCA diagnosis

On MRI, specific sequences such as diffusion-weighted imaging are not helpful in the differential diagnosis between iCCA and HCC and the MRI pattern of enhancement is similar to CT.

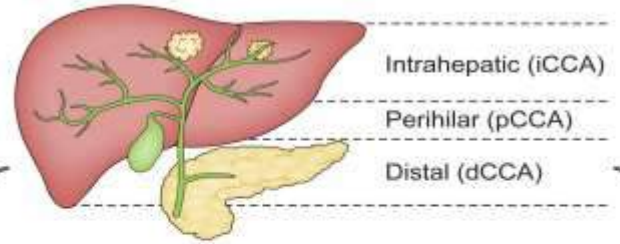
Intrahepatic cholangiocarcinoma with distinct boundary. (A-C) Computed tomography (CT) scan showing a low-density mass with a regular and distinct boundary. It is iso-attenuated relative to the liver on enhanced CT scans during the arterial (B) and portal venous phases (C). The black arrows point to the distinct boundary.




Suspected iCCA
Diagnosis
• Biopsy†
• IHC evaluation
Diagnosed iCCA
Staging
• MRI
• CT chest and abdomen
• PET scan
Resectable
Surgery
Adjuvant capecitabine
Unresectable
Systemic disease
Liver limited disease
Single lesion >2 cm or multinodular
Single lesion ≤2 cm
in a patient with cirrhosis
ECOG >2 and/or decompensated liver function
ECOG ≤2, preserved liver function
Evidence is lacking
Consider locoregional or systemic therapy
Consider liver transplant by protocol
Consider trans-arterial procedures or thermal ablation
Best supportive care
First-line systemic therapy
Gemcitabine/cisplatin/durvalumab
Progression
Genetic sequencing
Second-line systemic therapy
• FOLFOX
• FGFR inhibition*
• IDH inhibition*
• Immune checkpoint blockade for MSI-H/dMMR

Intrahepatic cholangiocarcinoma: Surgical management

Intrahepatic cholangiocarcinoma (iCCA) is a predominantly mass-forming and lymphophilic malignancy of the intrahepatic bile ducts. It is the second most common primary liver cancer after HCC. While relatively rare, the incidence of iCCA is increasing.



iCCA
- is increasing in incidence
- is usually diagnosed at a late stage
- has poor prognosis

Liver resection (LR)

LR is the only available curative treatment for iCCA, though only 12-40% of patients referred are resectable. Overall survival at 5-years is 25-40%, and 50-70% face tumor recurrence.

Liver transplant (LT)

Currently not a standard therapy!

Retrospective studies are now being conducted with more stringent selection criteria. One major study found a 5-year overall survival of 65% after transplantation for single tumors ≤2 cm.

Selection

Selection of candidates for liver resection is based on oncological-, patient-, and liver-related factors

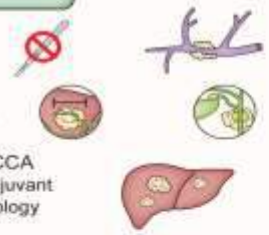
Indications
- FLR >25% in normal liver
- FLR >40% in chronic liver disease
- High quality FLR
- Solitary iCCA
- Peripheral/accessible location (Low morbidity/mortality)

Contraindications
- FLR <25% in normal liver
- FLR <40% in chronic liver disease
- Low quality FLR (Steatosis, atrophy, cirrhosis, fibrosis) (relative)
- Peritoneal/distant metastasis
- Distant lymph node involvement
- Central location (relative) (High morbidity/mortality)
- Portal hypertension (relative)

Selection

Use of LT in iCCA and selection criteria for these patients is under active study. LT is considered for patients that are unresectable due to location, liver dysfunction, or bilobar disease

Indications
- Unresectable (ex. cirrhotic FLR)
- Early stage iCCA (Single tumor ≤2 cm)
- Locally advanced iCCA
  - Response to neoadjuvant
  - Favorable tumor biology



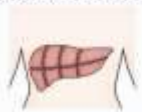
Contraindications
- Vascular invasion
- Extrahepatic disease
- Lymph node spread
- Locally advanced iCCA
  - No response to neoadjuvant
  - Unfavorable tumor biology

Surgery

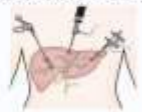
Operative technique is a focus for research to improve outcomes and increase resectability

Ideal...

Anatomic resection



Laparoscopic resection



Lymphadenectomy (≥6 nodes for staging)

Consider...

Vascular resection
- For infiltrative iCCA
- Comparable outcomes

Repeat resection
- For recurrent iCCA
- Acceptable morbidity/mortality

Surgery

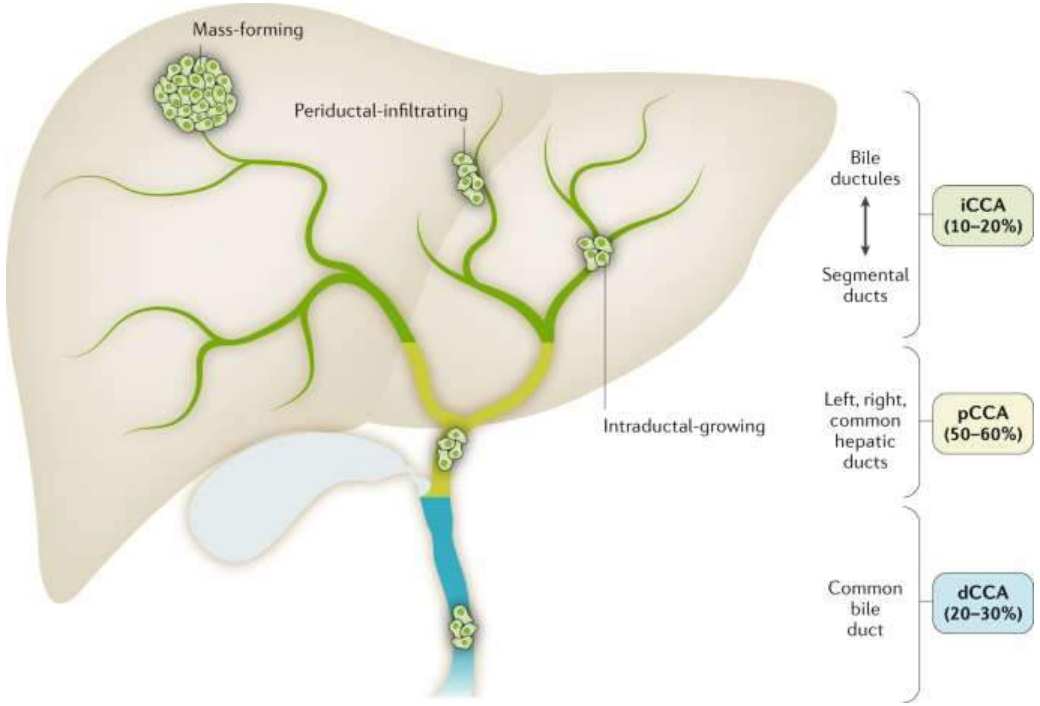
Consider the source of a donor liver and pre-transplant lymph node procurement

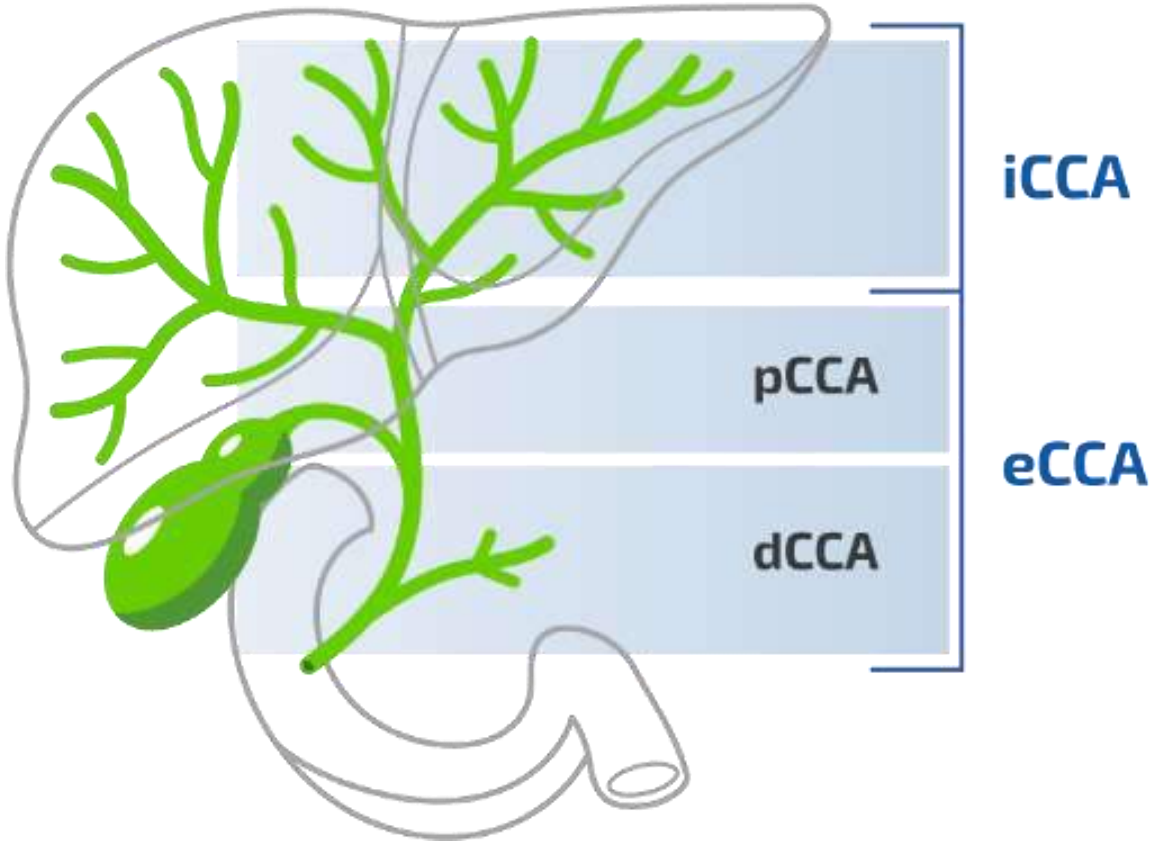
Living donor liver transplant *vs.* Deceased donor liver transplant

Portal lymphadenectomy

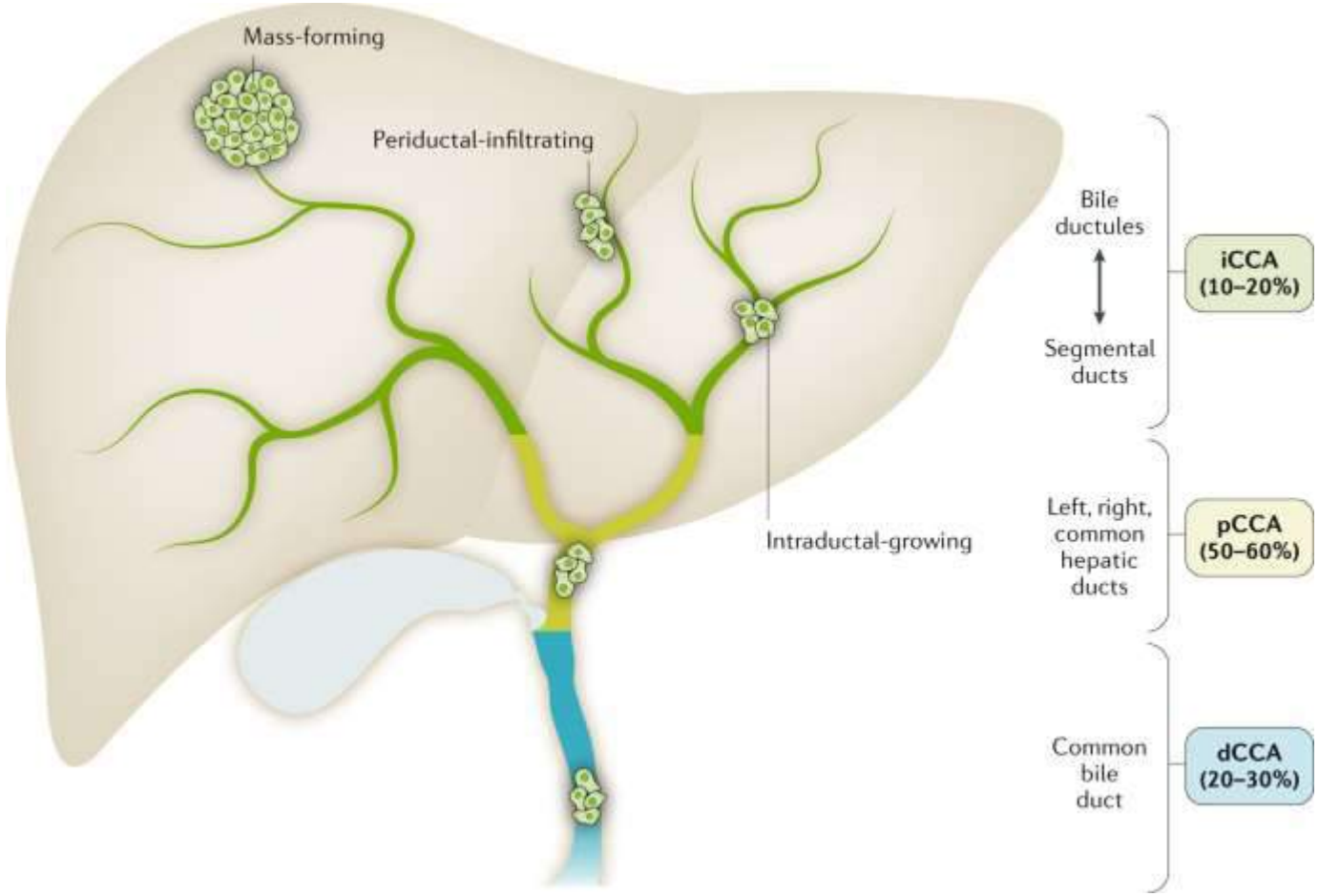
Staging and prognosis

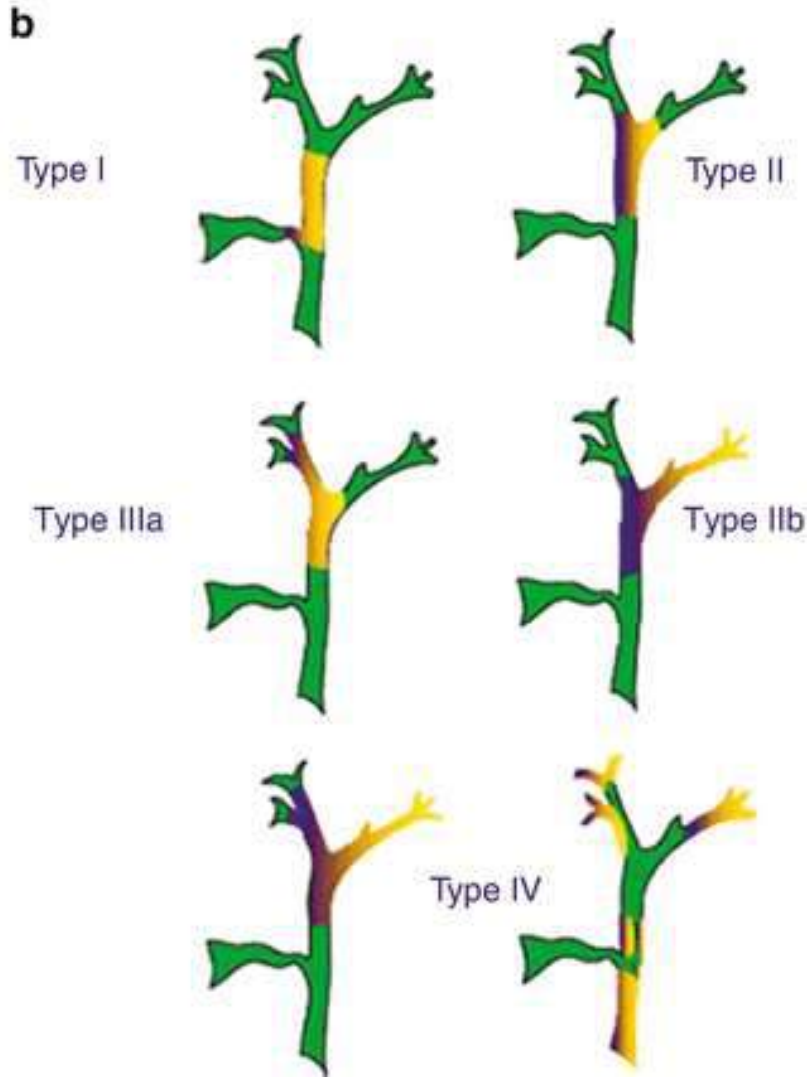
CCA

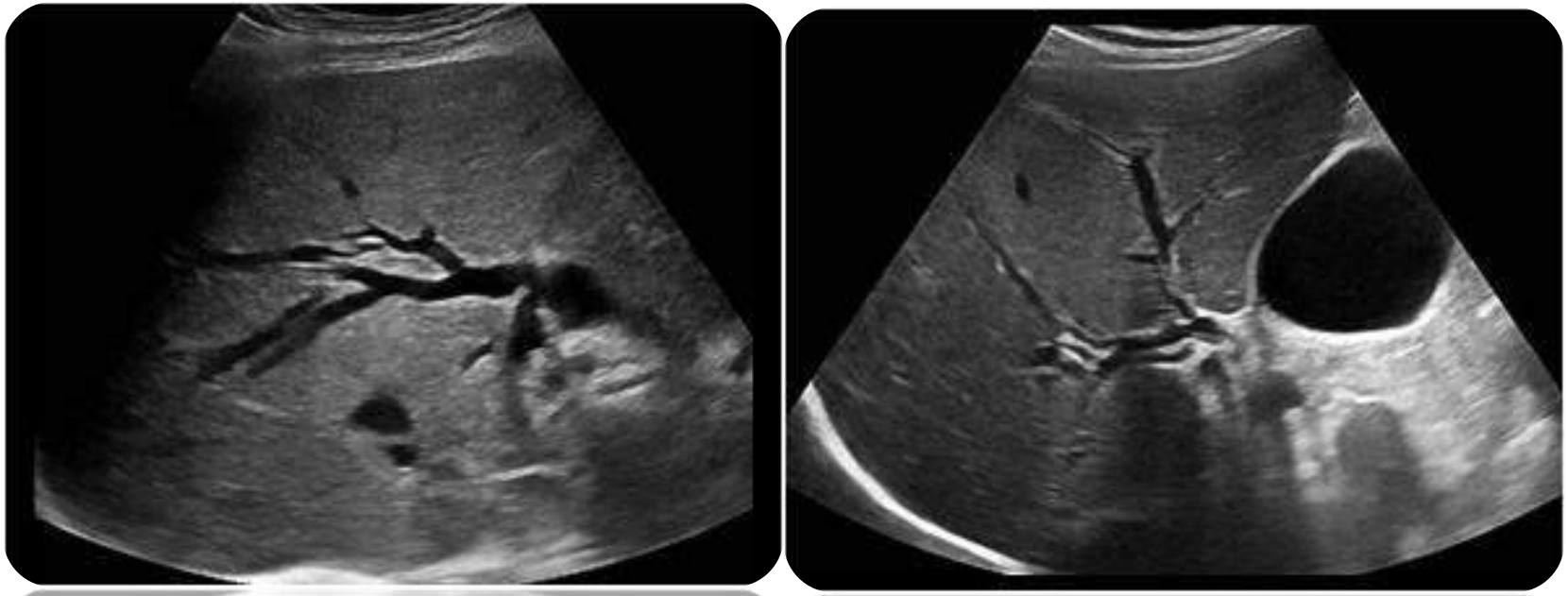

Mass-forming
Periductal-infiltrating
Intraductal-growing
Bile ductules
Segmental ducts
iCCA (10–20%)
Left, right, common hepatic ducts
pCCA (50–60%)
Common bile duct
dCCA (20–30%)

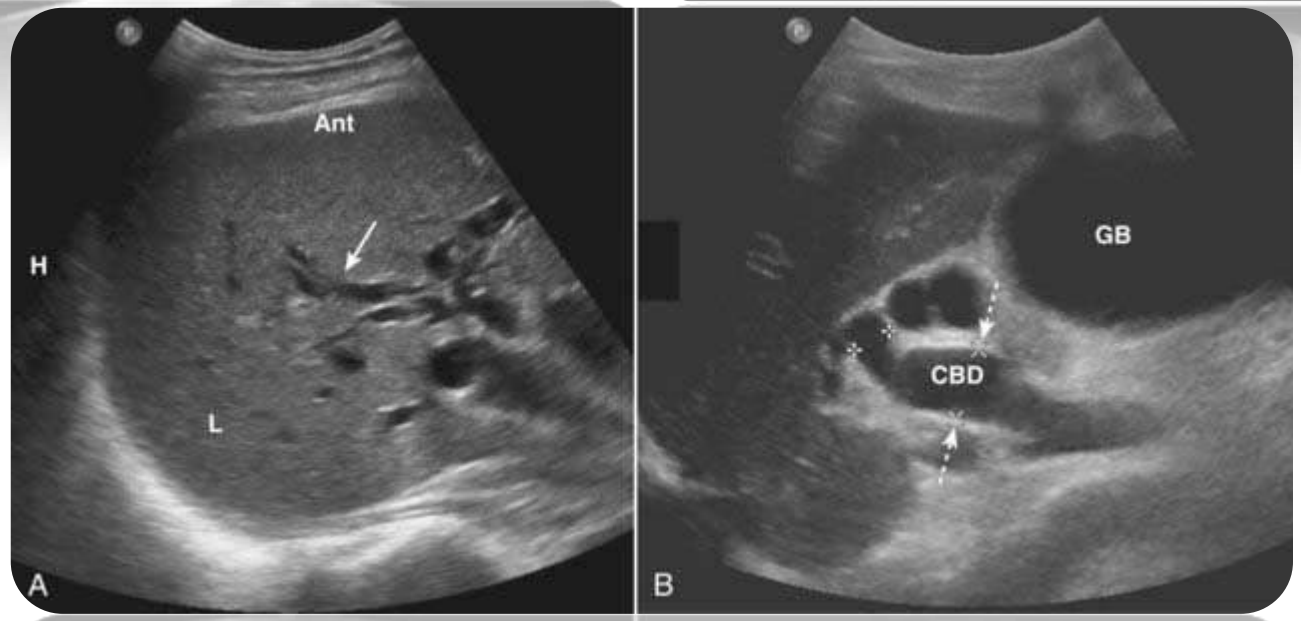

iCCA
pCCA
eCCA
dCCA

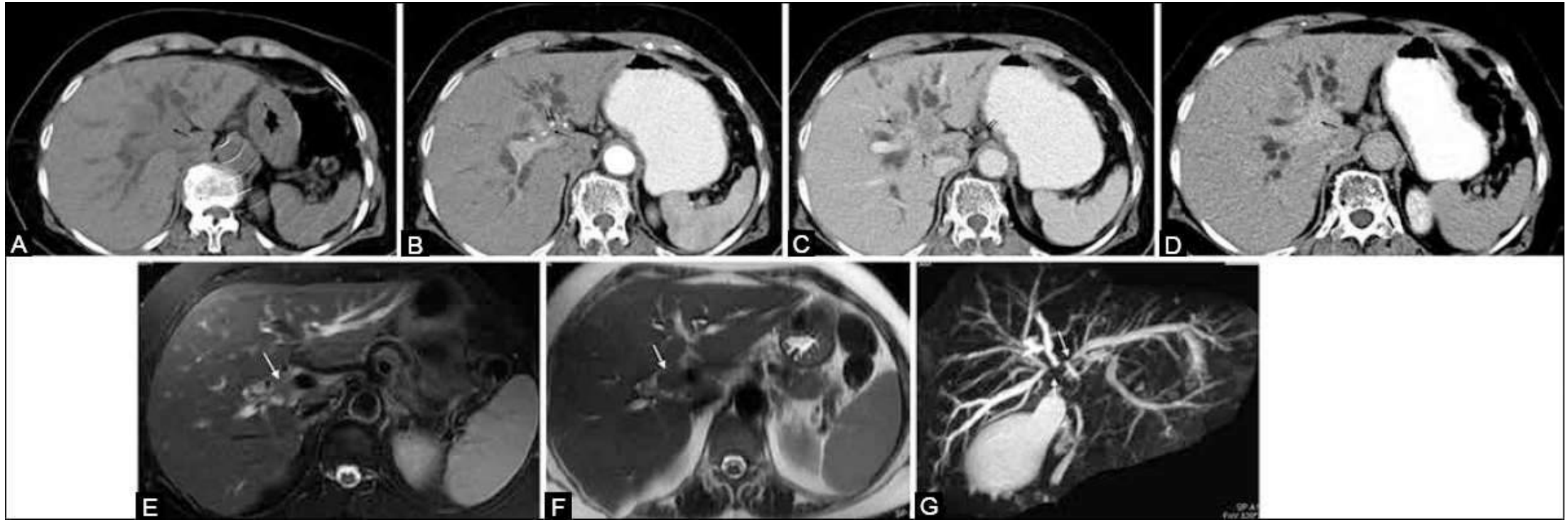
Anatomical classification of proximal and distal CCA (Klatskin Tumor)

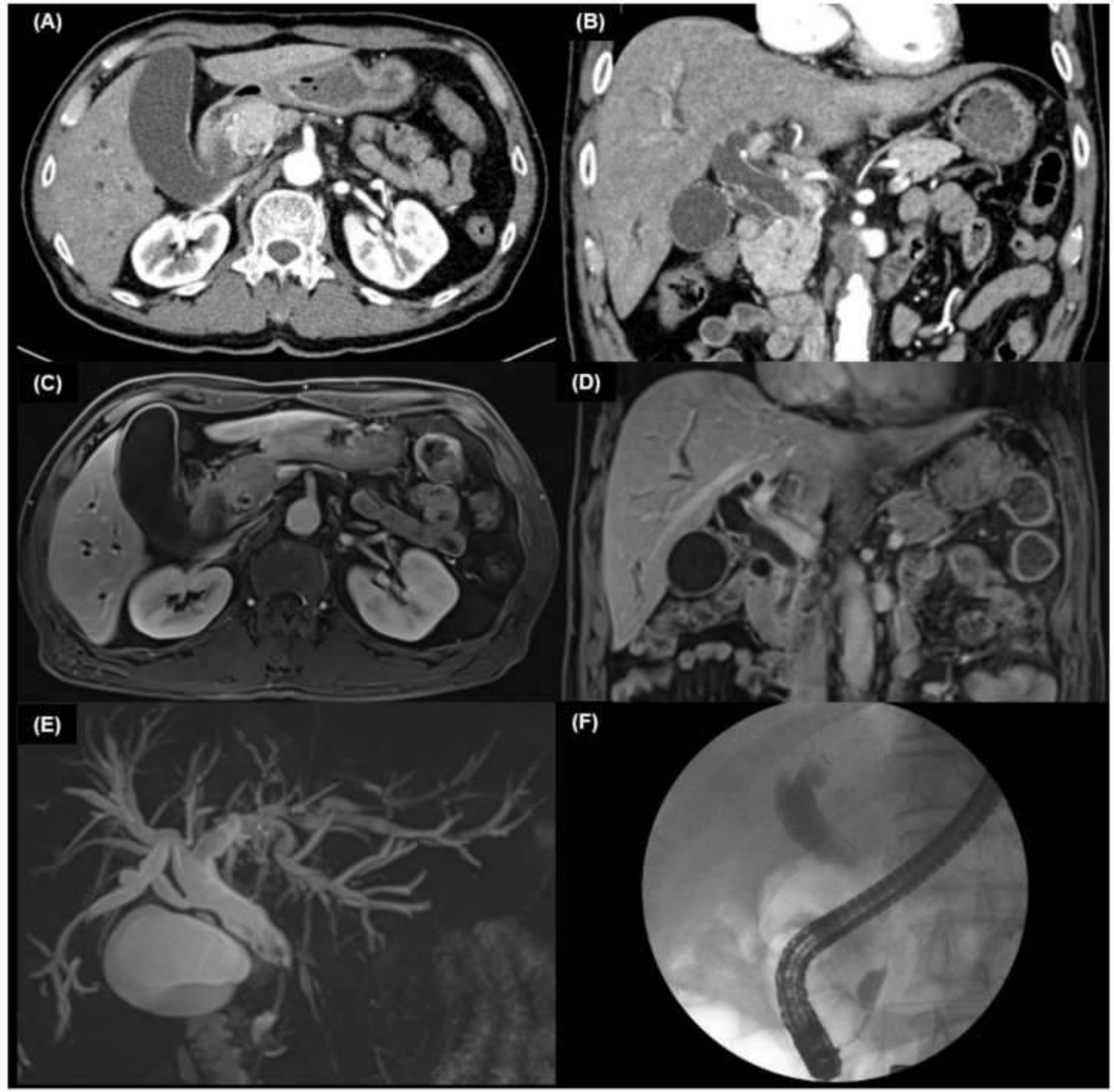




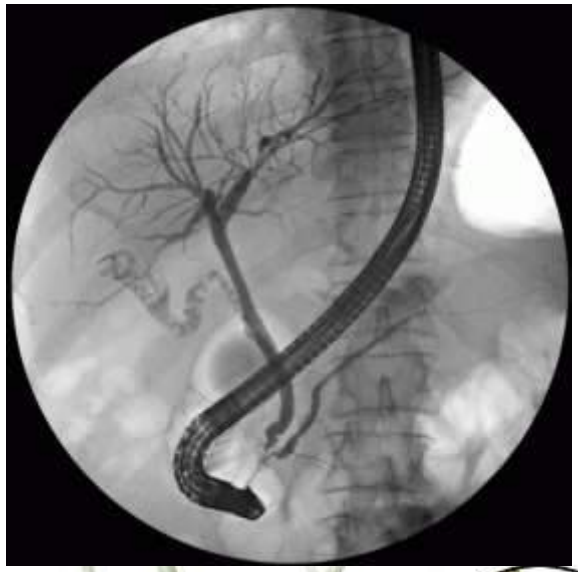


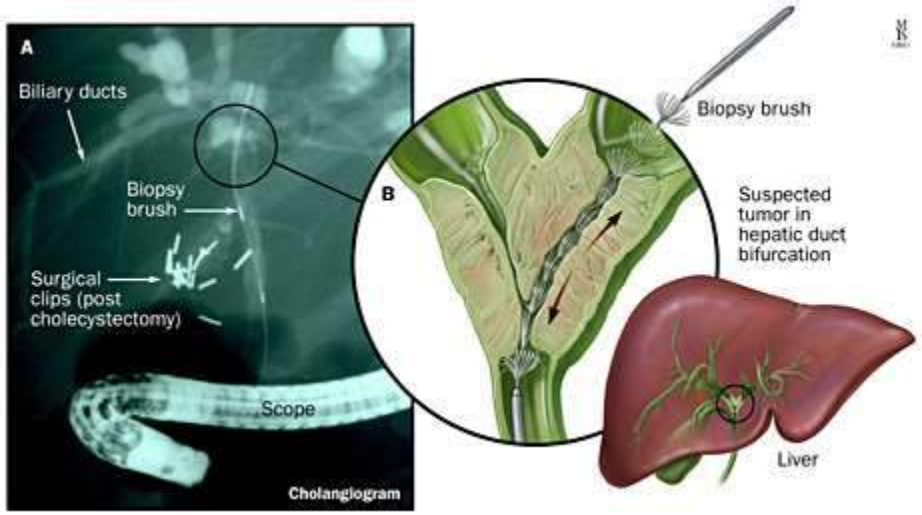

Ant
H
L
A
GB
CBD
B

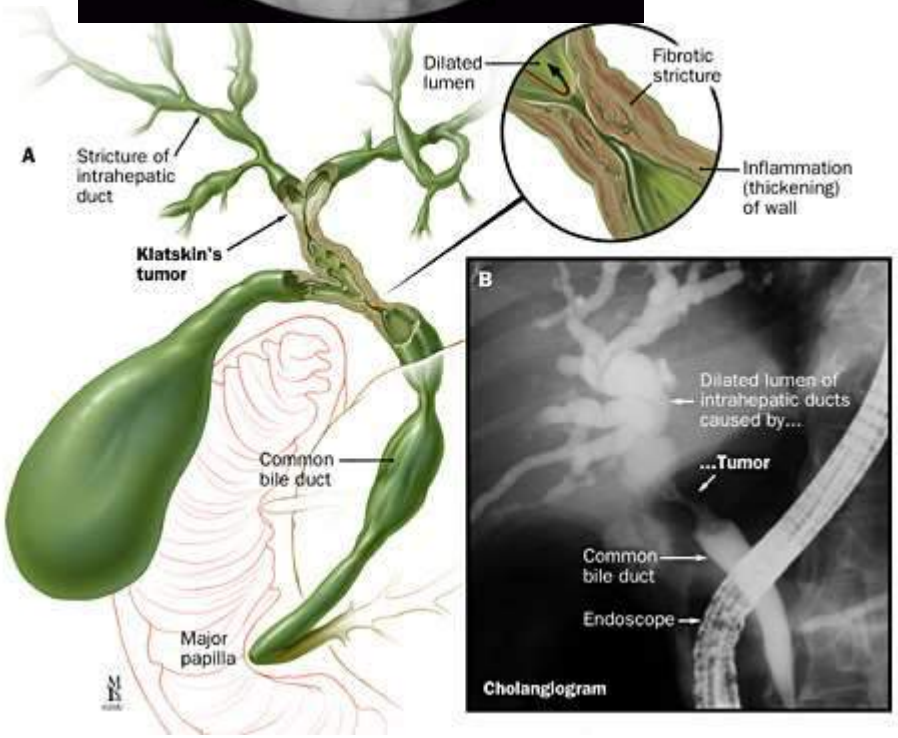

A
B
C
D
E
F
G

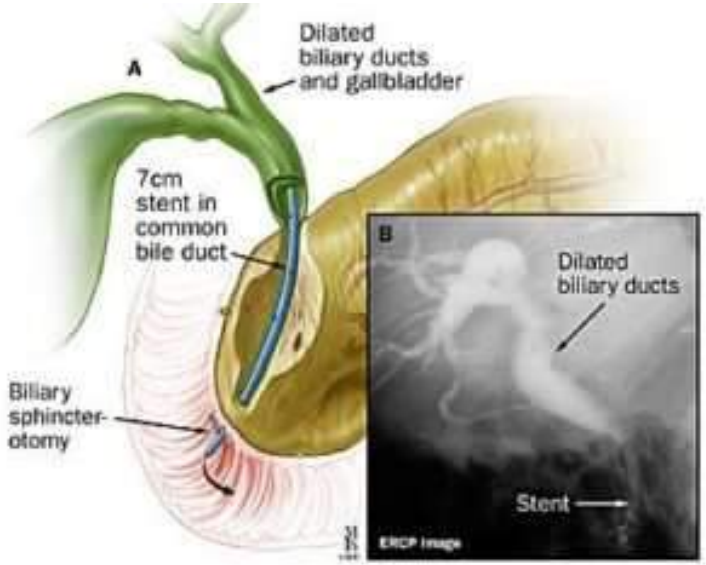

(A)
(B)
(C)
(D)
(E)
(F)

ERCP

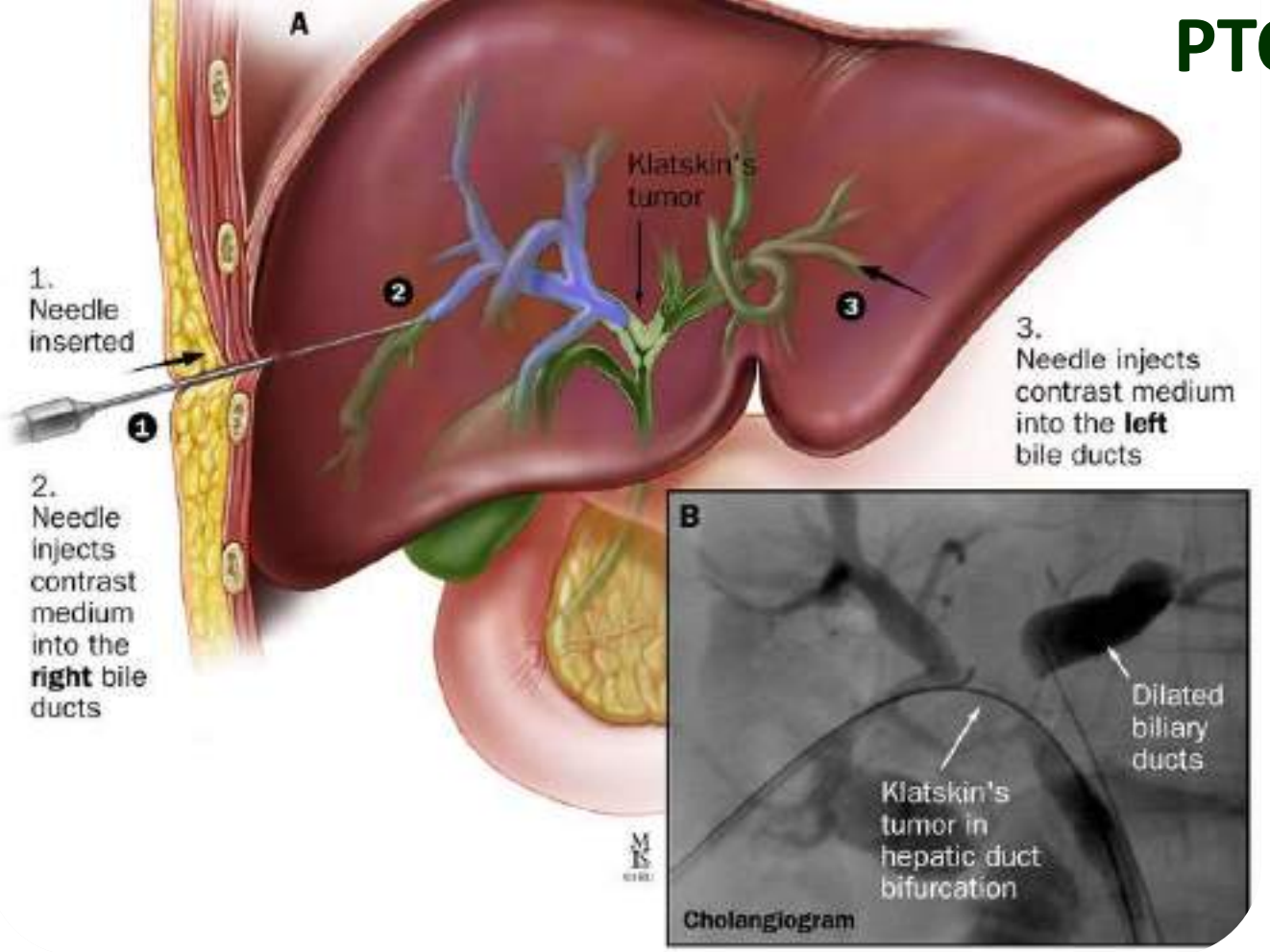



A
Biliary ducts
Biopsy brush
Surgical clips (post cholecystectomy)
Scope
Cholangiogram
B
Biopsy brush
Suspected tumor in hepatic duct bifurcation
Liver

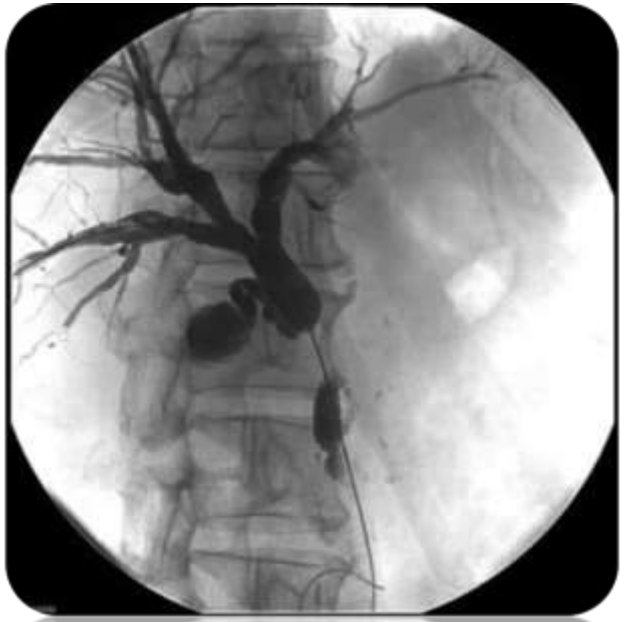

A
Stricture of intrahepatic duct
Klatskin's tumor
Dilated lumen
Fibrotic stricture
Inflammation (thickening) of wall
Common bile duct
Major papilla
B
Dilated lumen of intrahepatic ducts caused by...
...Tumor
Common bile duct
Endoscope
Cholangiogram

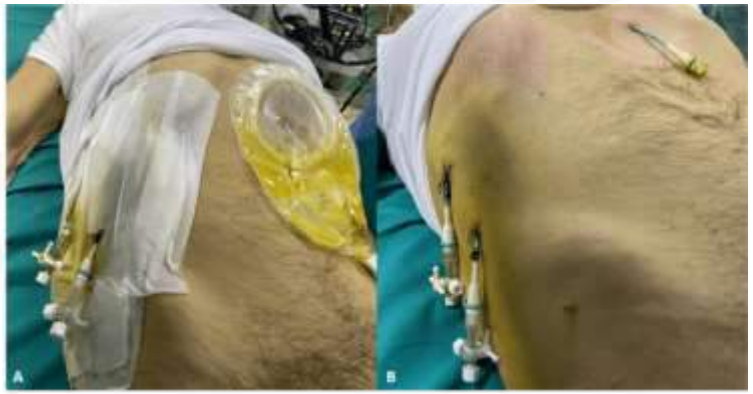

A
Dilated biliary ducts and gallbladder
7cm stent in common bile duct
Biliary sphincter-otomy
B
Dilated biliary ducts
Stent

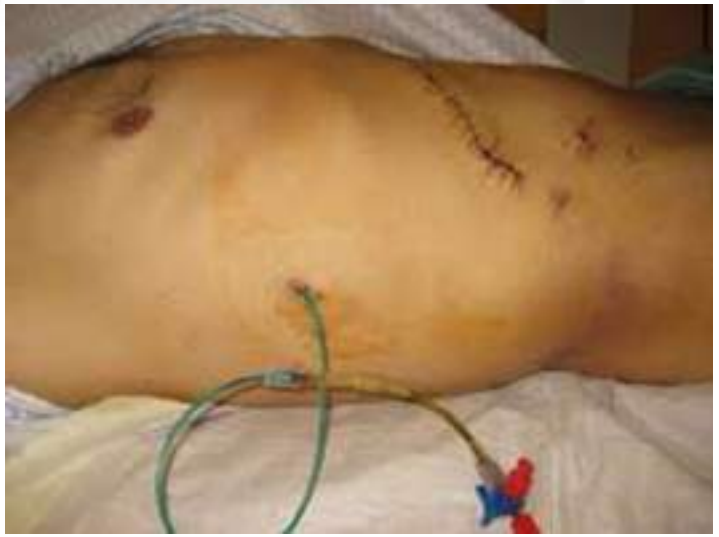
PTC


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

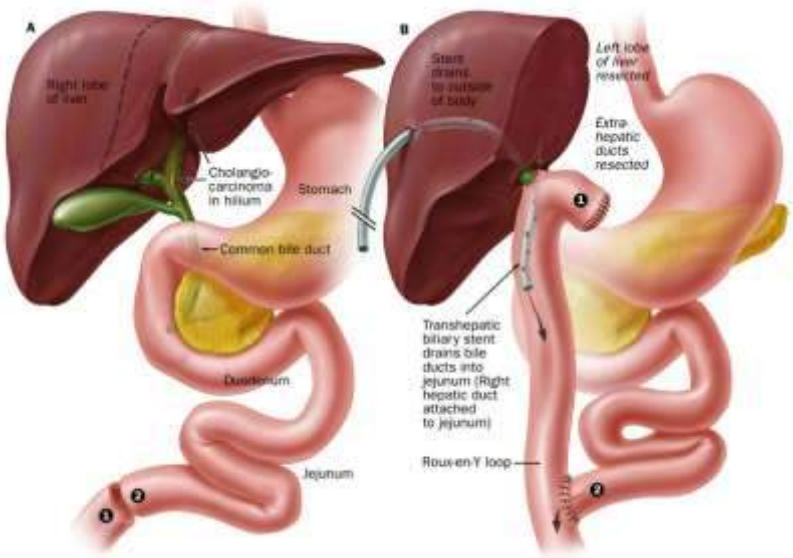
B
Dilated biliary ducts
Klatskin's tumor in hepatic duct bifurcation
Cholangiogram

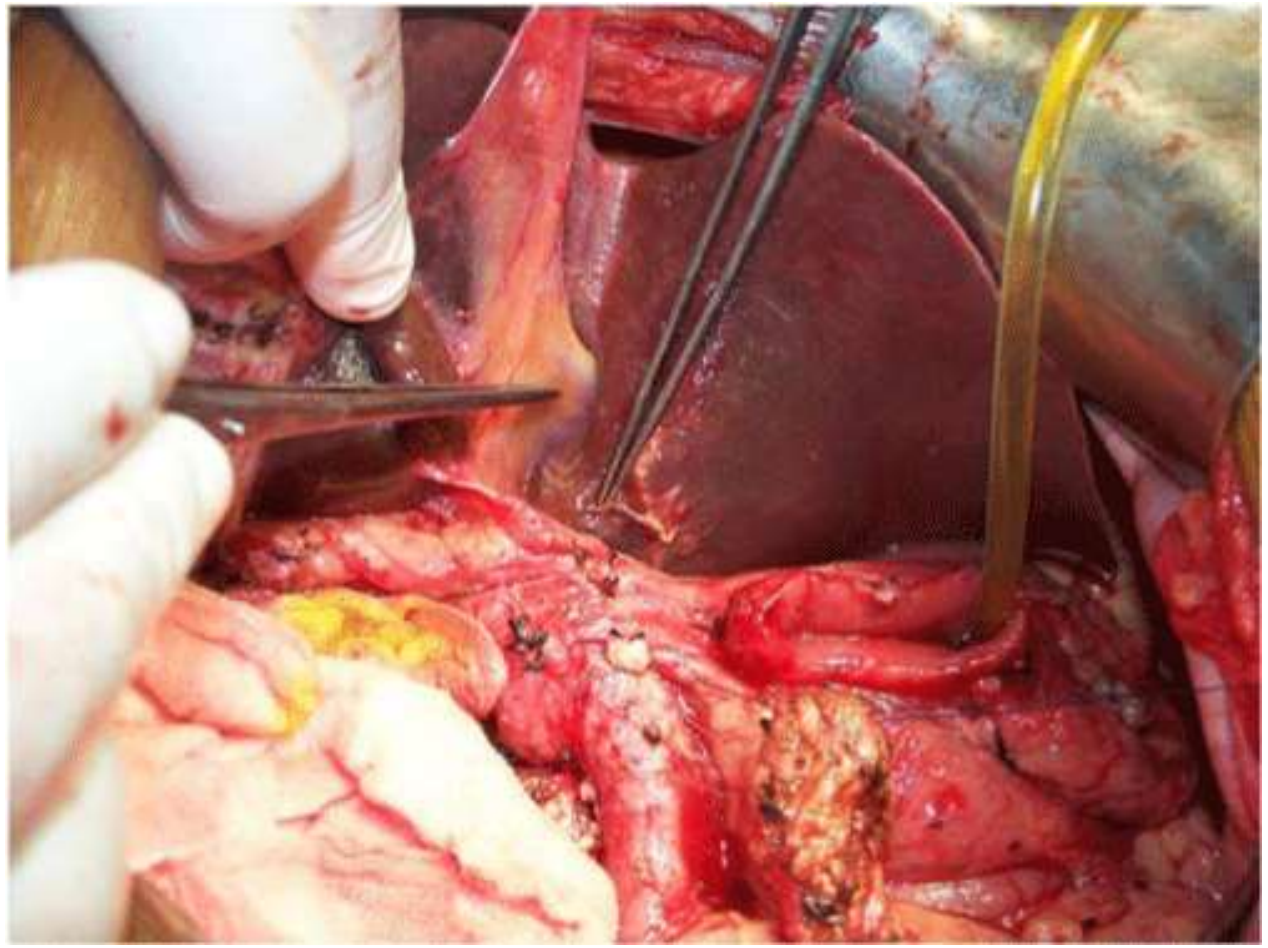






SURGERY


A
Right lobe of liver
Cholangio-carcinoma in hilium
Stomach
Common bile duct
Duodenum
Jejunum
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



CCA overall survival rate