In the name of God

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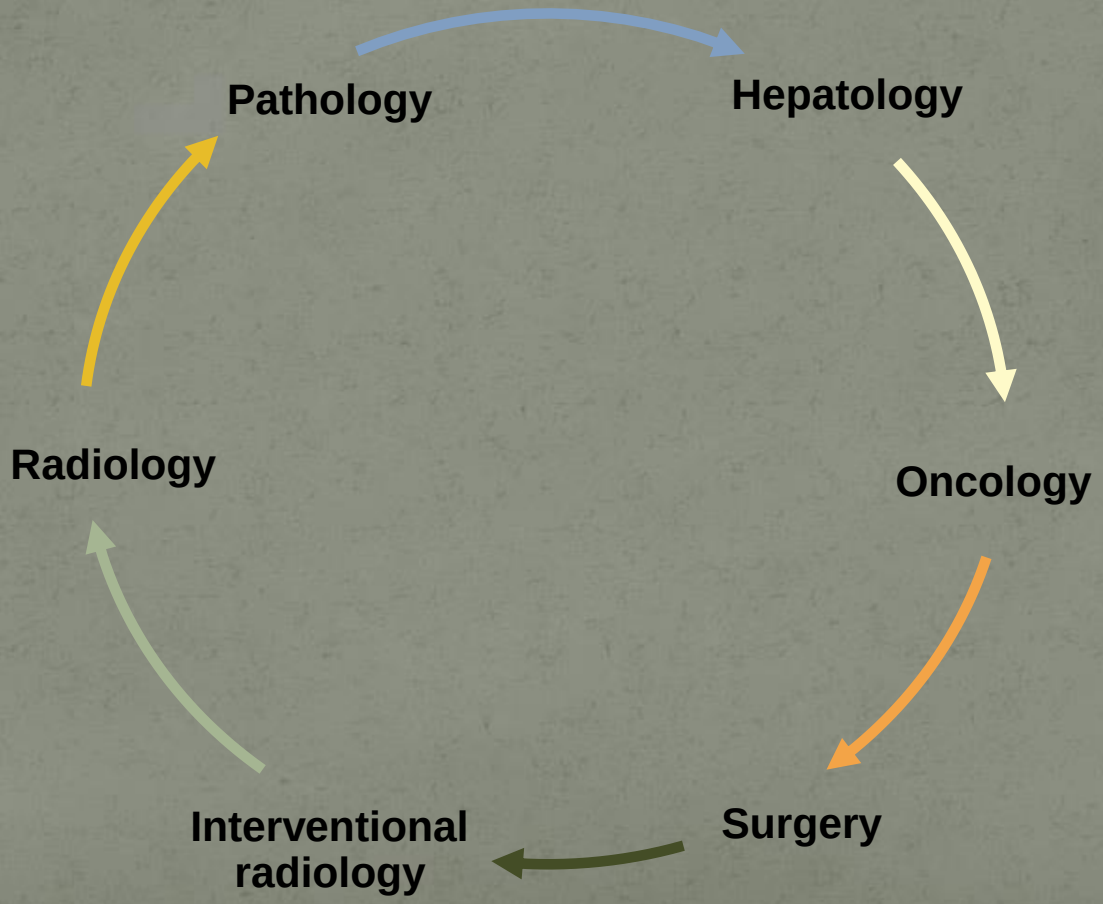
Multidisciplinary Approach to the Patient With Hepatic Tumors



-TACE

1.cTACE

2.DEB-TACE

- TARE

-Thermal ablations

HCC

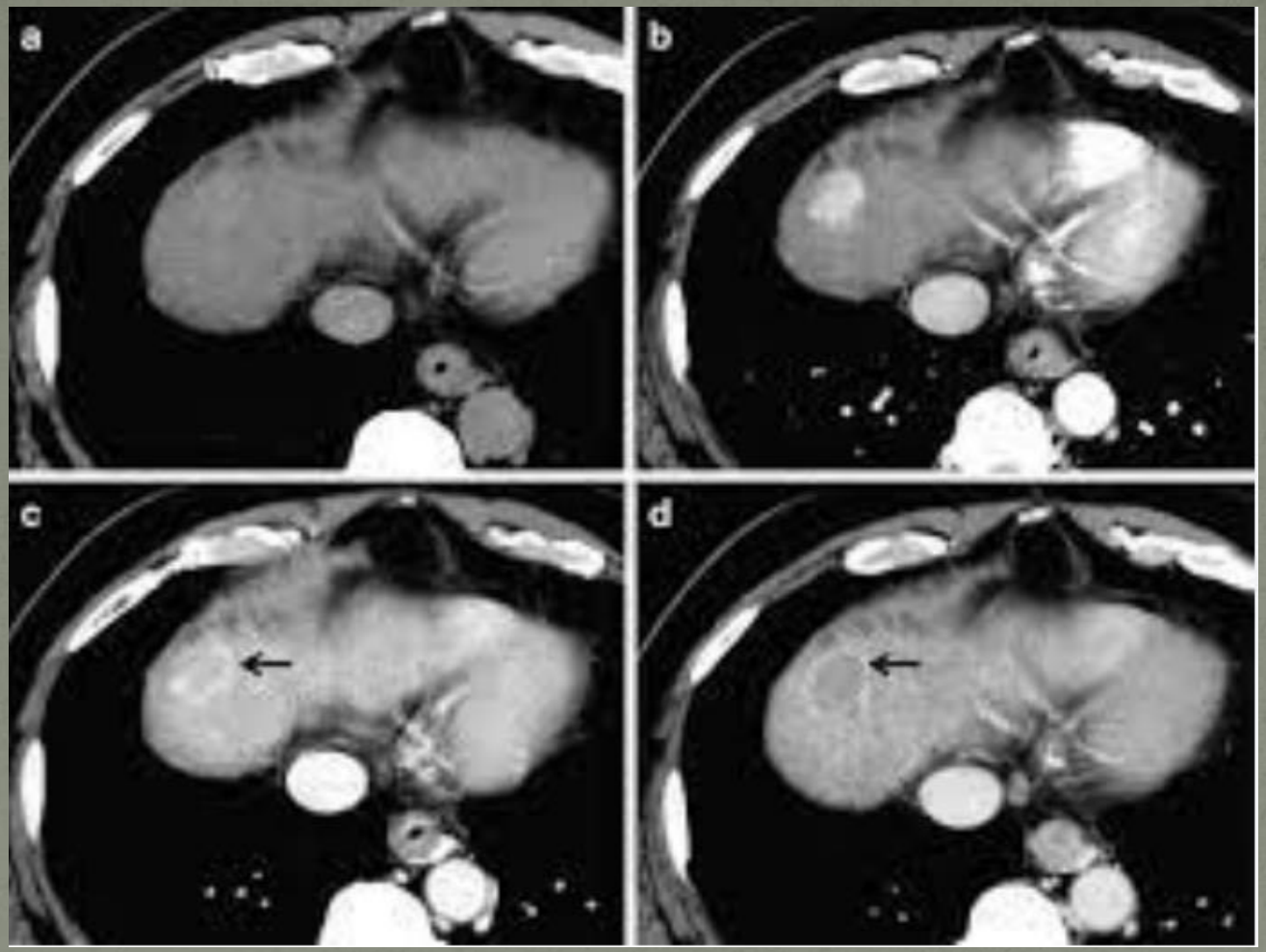
Diagnosis

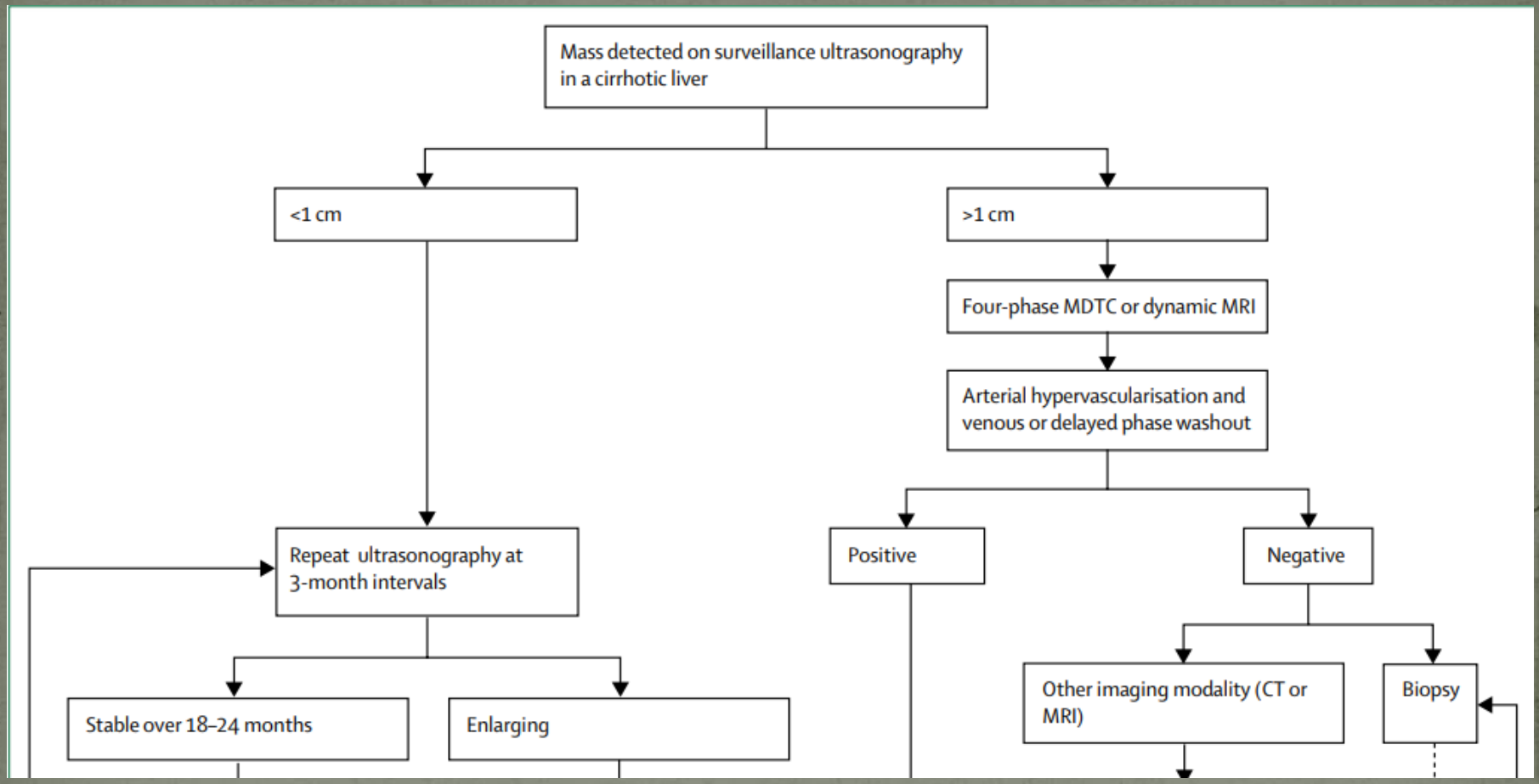
1. Non-invasive diagnosis

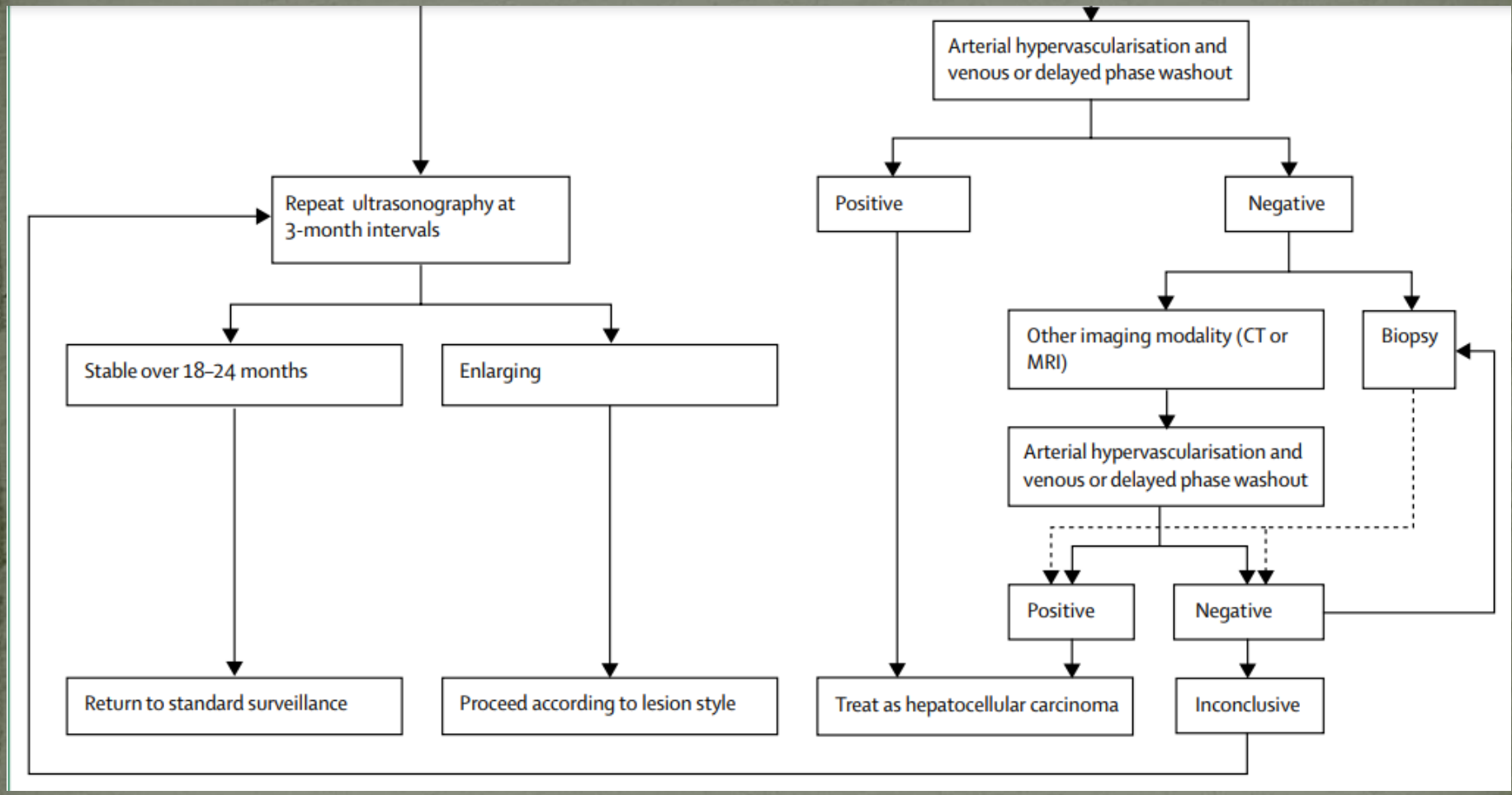
- HCC can be diagnosed with characteristic findings on dynamic CT or dynamic MRI (i.e. hypervascularity in the arterial phase and washout in the portal venous or delayed phase)

2.Pathological diagnosis

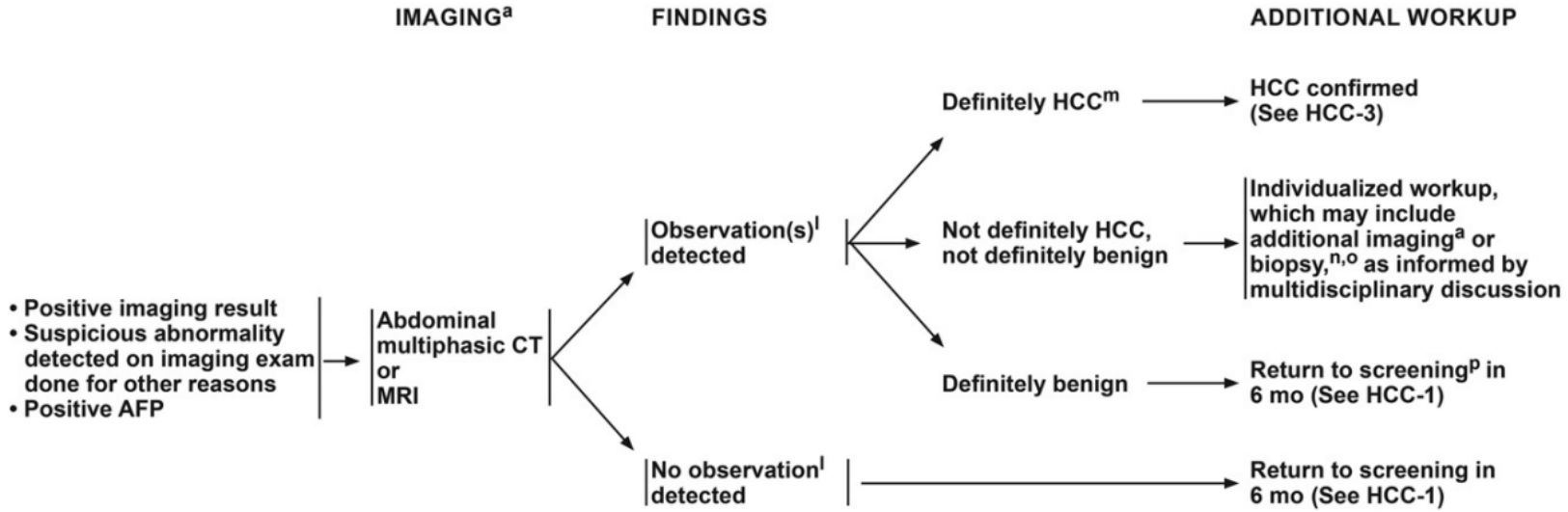
is recommended by all 8 guidelines if imaging diagnosis does not
disclose characteristic features of HCC


a
b
c
d


Mass detected on surveillance ultrasonography in a cirrhotic liver
<1 cm
>1 cm
Four-phase MDTC or dynamic MRI
Arterial hypervascularisation and venous or delayed phase washout
Positive
Negative
Repeat ultrasonography at 3-month intervals
Stable over 18–24 months
Enlarging
Other imaging modality (CT or MRI)
Biopsy


Arterial hypervascularisation and venous or delayed phase washout
Positive
Negative
Repeat ultrasonography at 3-month intervals
Other imaging modality (CT or MRI)
Biopsy
Stable over 18–24 months
Enlarging
Arterial hypervascularisation and venous or delayed phase washout
Positive
Negative
Return to standard surveillance
Proceed according to lesion style
Treat as hepatocellular carcinoma
Inconclusive

DIAGNOSIS OF HCC[b]



[a] See Principles of Imaging (HCC-A*).
[b] Adapted with permission from Marrero JA, Kulik LM, Sirlin C, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. Hepatology 2018;68:723-750.
[l] An observation is an area identified at imaging that is distinctive from background liver. It may be a mass or a pseudo lesion.
[m] Criteria for observations that are definitely HCC have been proposed by LI-RADS and adopted by AASLD. These criteria apply only to patients at high risk for HCC. OPTN has proposed imaging criteria for HCC applicable in candidates for liver transplant. See Principles of Imaging (HCC-A*).
[n] Before biopsy, evaluate if patient is a resection or transplant candidate. If patient is a potential transplant candidate, consider referral to transplant center before biopsy.
[o] See Principles of Biopsy (HCC-B*).
[p] If no observations are detected at diagnostic imaging despite positive surveillance tests, then return to surveillance in 6 months if the most reasonable explanation is that surveillance tests were false positive. Consider imaging with an alternative method +/- AFP if there is reasonable suspicion that the diagnostic imaging test was false negative.

*Available online, in these guidelines, at NCCN.org.

Staging systems

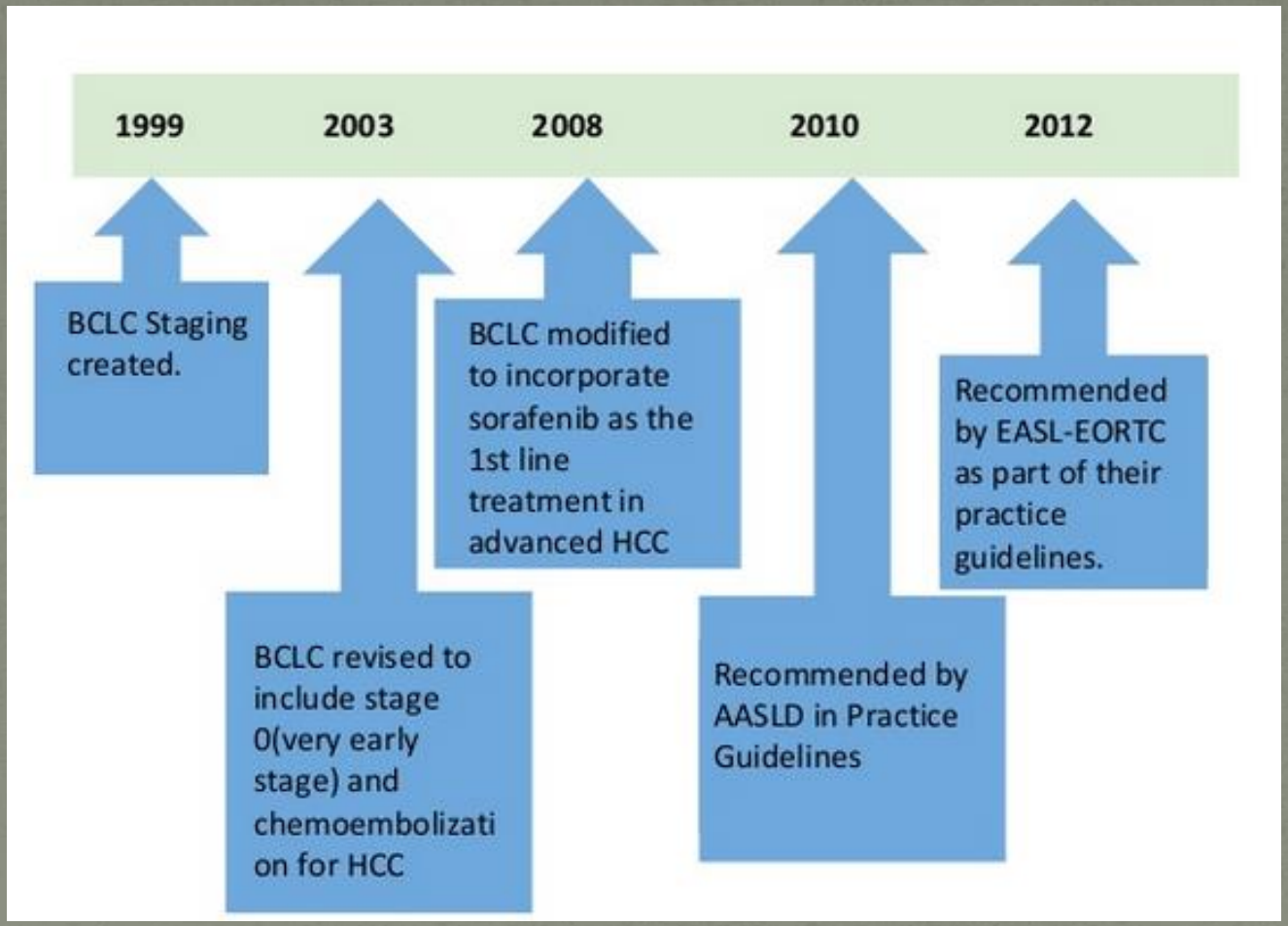
- Okuda stage
- French score
- CLIP score
- BCLC staging
- CUPI score
- TNM staging
- JIS score
- ER score.

- The Barcelona-Clinic Liver Cancer (BCLC) staging system has appeared as the most popular to guide treatment decision and has been endorsed by many guidelines including AASLD, EASL-EORTC, and ESMO-ESDO [with two modifications]

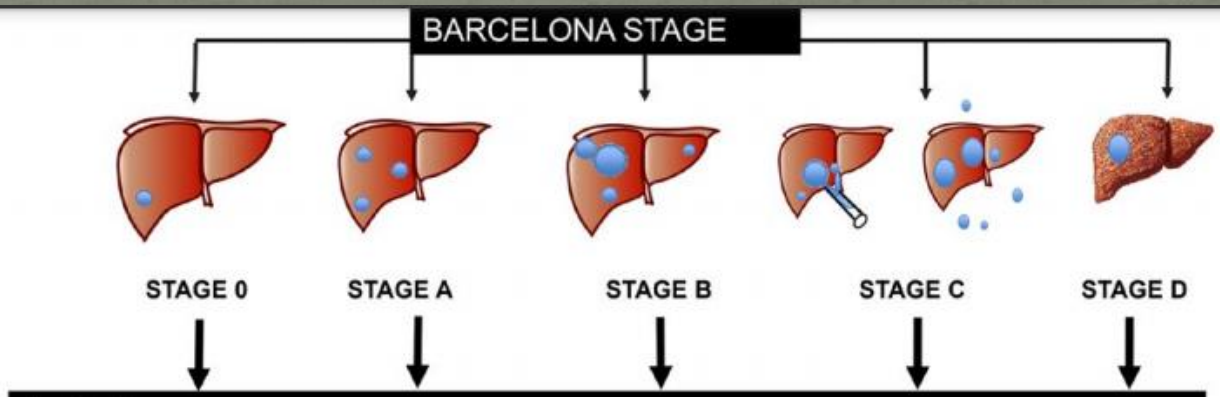

BCLC
BARCELONA
CLINIC
LIVER
CANCER

The BCLC at the Hospital Clínic of Barcelona is a multidisciplinary team involving all relevant medical specialities devoted to clinical care, research and education in the field of liver cancer. It combines state of the art diagnosis and therapy, with the development of several research projects to evaluate new treatment options. These include laboratory studies in cell cultures or animal models and clinical trials in patients with liver cancer.

The BCLC group was created in 1986 by Jordi Bruix (Hepatologist) and Concepció Bru (Radiologist devoted to ultrasound). The initial studies focused on clinical issues related to the epidemiology, diagnosis and natural history of liver cancer. The need to incorporate expertise and knowledge in different fields primed the incorporation of physicians working in pathology (Manel Solé), computed tomography and magnetic resonance (Carmen Ayuso), Hepatic Surgery (Josep Fuster) and Vascular Radiology and Intervention (Xavier Montanyà and Maribel Real).

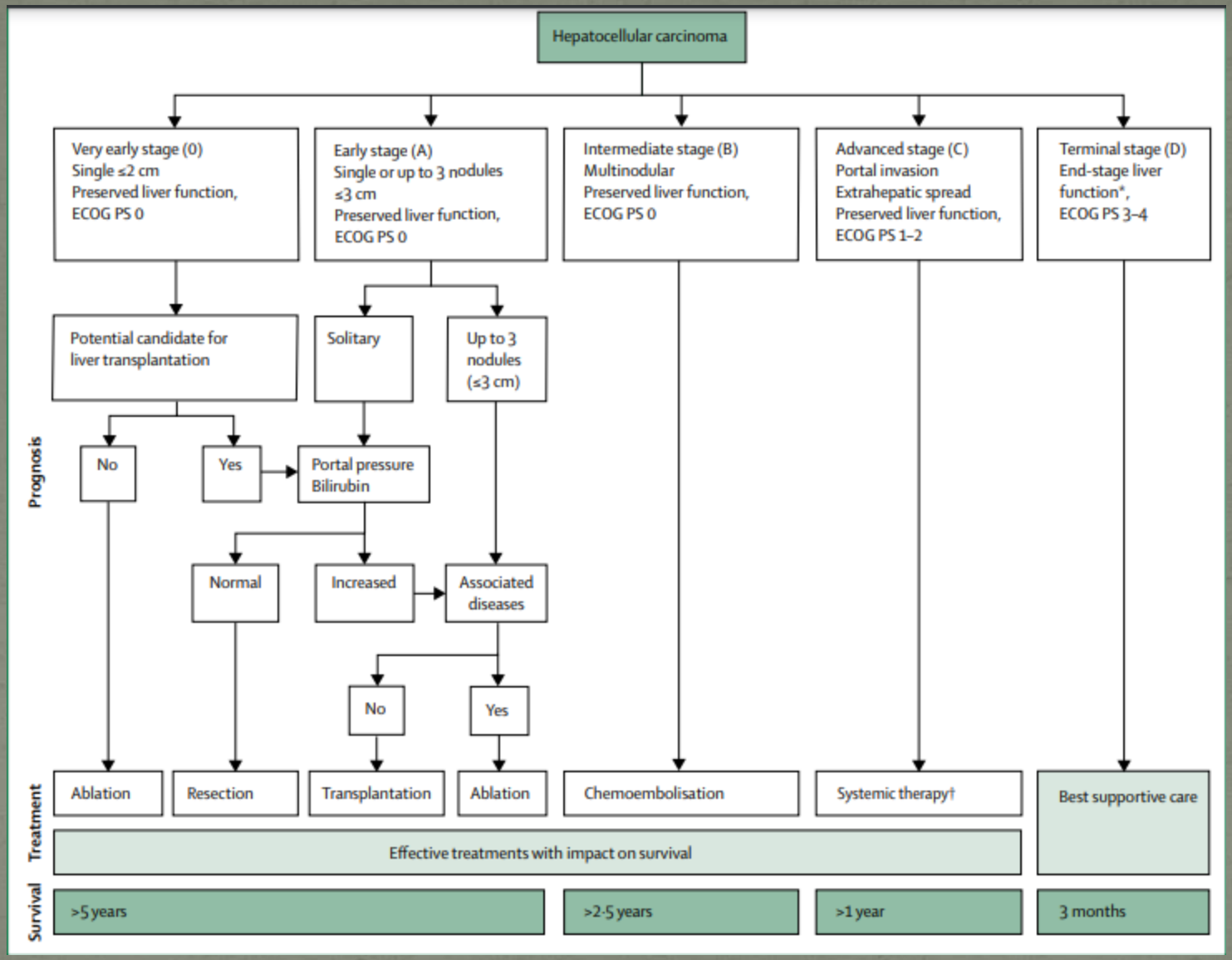

1999
2003
2008
2010
2012
BCLC Staging created.
BCLC revised to include stage 0(very early stage) and chemoembolizati on for HCC
BCLC modified to incorporate sorafenib as the 1st line treatment in advanced HCC
Recommended by AASLD in Practice Guidelines
Recommended by EASL-EORTC as part of their practice guidelines.

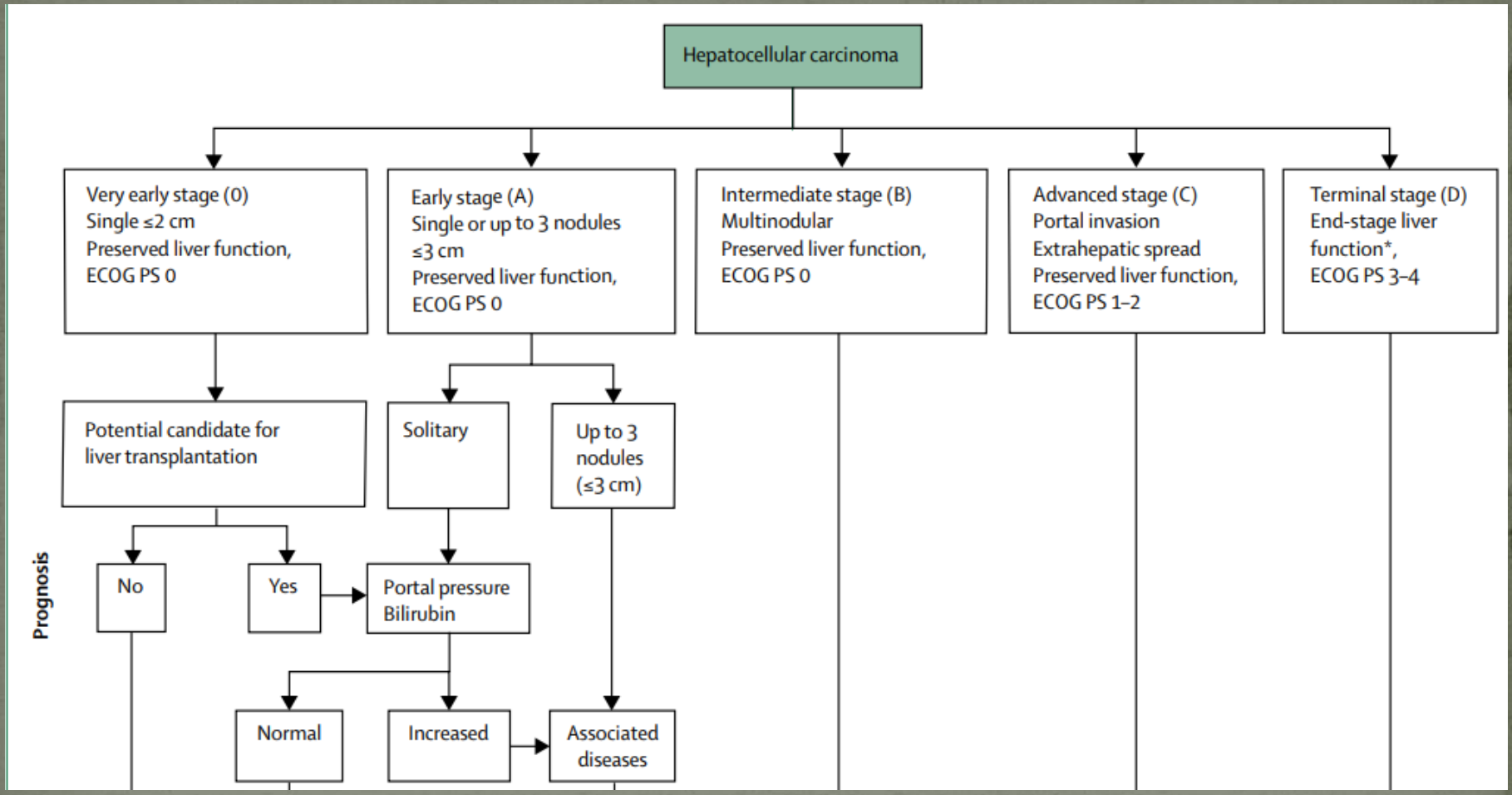

Diagnosis
BCLC 0
BCLC A
BCLC B
BCLC C
BCLC D
Surgery
Ablation
TACE
sorafenib
BSC
DEATH



Level of Evidence					
1	Resection		TACE	Sorafenib (1L) Lenvatinib (1L) Regorafenib (2L) Cabozantinib (2L)	
2	RFA MWA	Resection OLT RFA MWA TARE TACE SBRT	TARE Downsize OLT	Nivolumab (2L)	OLT BSC
3				TARE	

FIG. 3. Treatment recommendations according to BCLC Stage. Abbreviations: MWA, microwave ablation; BSC, best supportive care; 1L, first-line therapy; 2L, second-line therapy.


Hepatocellular carcinoma
Very early stage (0)
Single ≤2 cm
Preserved liver function,
ECOG PS 0
Early stage (A)
Single or up to 3 nodules
≤3 cm
Preserved liver function,
ECOG PS 0
Intermediate stage (B)
Multinodular
Preserved liver function,
ECOG PS 0
Advanced stage (C)
Portal invasion
Extrahepatic spread
Preserved liver function,
ECOG PS 1–2
Terminal stage (D)
End-stage liver
function*,
ECOG PS 3–4
Potential candidate for
liver transplantation
Solitary
Up to 3
nodules
(≤3 cm)
No
Yes
Portal pressure
Bilirubin
Normal
Increased
Associated
diseases
No
Yes
Prognosis
Ablation
Resection
Transplantation
Ablation
Chemoembolisation
Systemic therapy†
Best supportive care
Treatment
Effective treatments with impact on survival
Survival
>5 years
>2·5 years
>1 year
3 months


Hepatocellular carcinoma
Very early stage (0)
Single ≤2 cm
Preserved liver function,
ECOG PS 0
Early stage (A)
Single or up to 3 nodules
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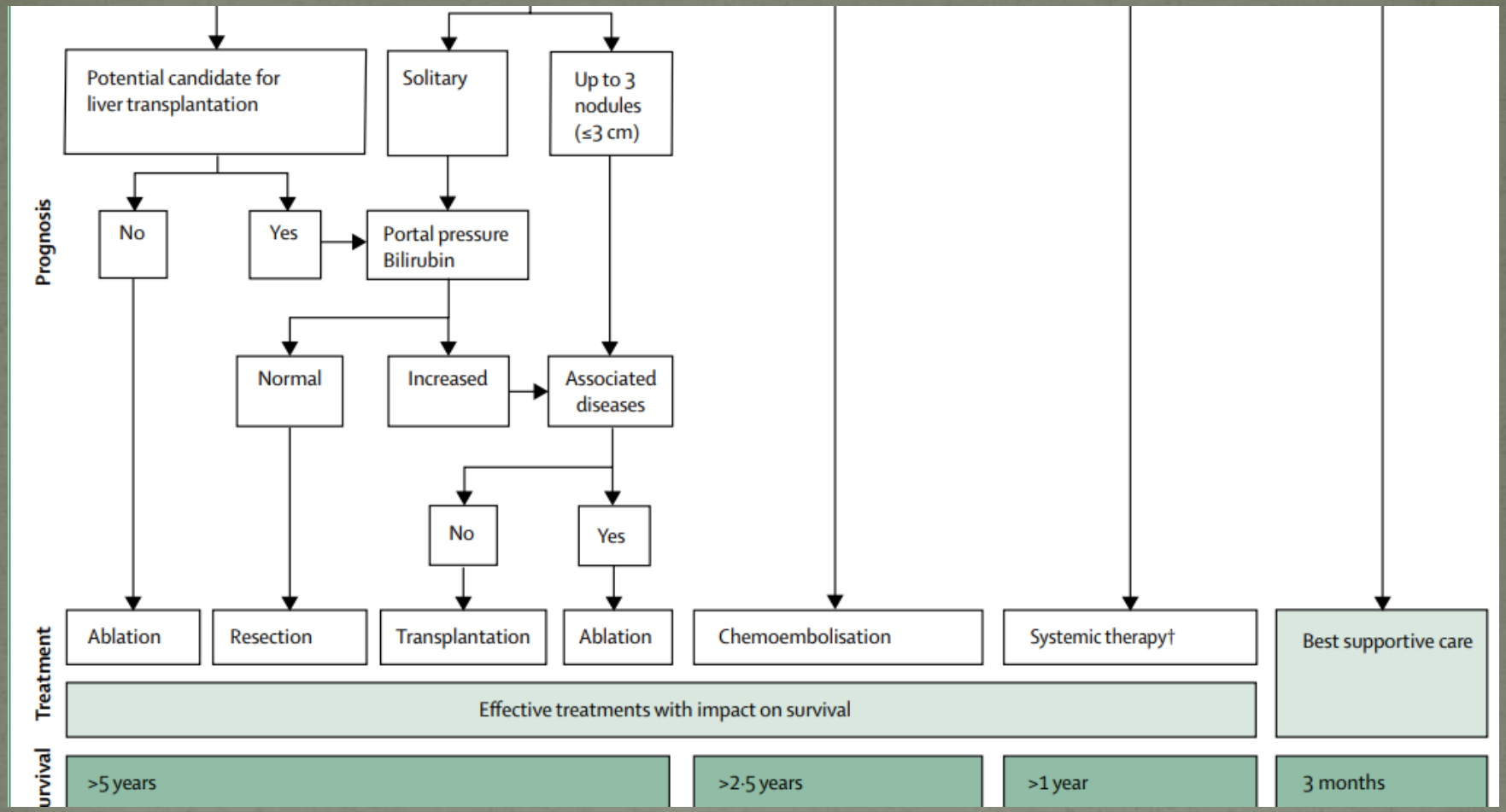
Preserved liver function,
ECOG PS 0
Intermediate stage (B)
Multinodular
Preserved liver function,
ECOG PS 0
Advanced stage (C)
Portal invasion
Extrahepatic spread
Preserved liver function,
ECOG PS 1–2
Terminal stage (D)
End-stage liver
function*,
ECOG PS 3–4
Potential candidate for
liver transplantation
Solitary
Up to 3
nodules
(≤3 cm)
Prognosis
No
Yes
Portal pressure
Bilirubin
Normal
Increased
Associated
diseases


Potential candidate for liver transplantation
Solitary
Up to 3 nodules (≤3 cm)
Prognosis
No
Yes
Portal pressure Bilirubin
Normal
Increased
Associated diseases
No
Yes
Treatment
Ablation
Resection
Transplantation
Ablation
Chemoembolisation
Systemic therapy†
Best supportive care
Effective treatments with impact on survival
urvival
>5 years
>2·5 years
>1 year
3 months

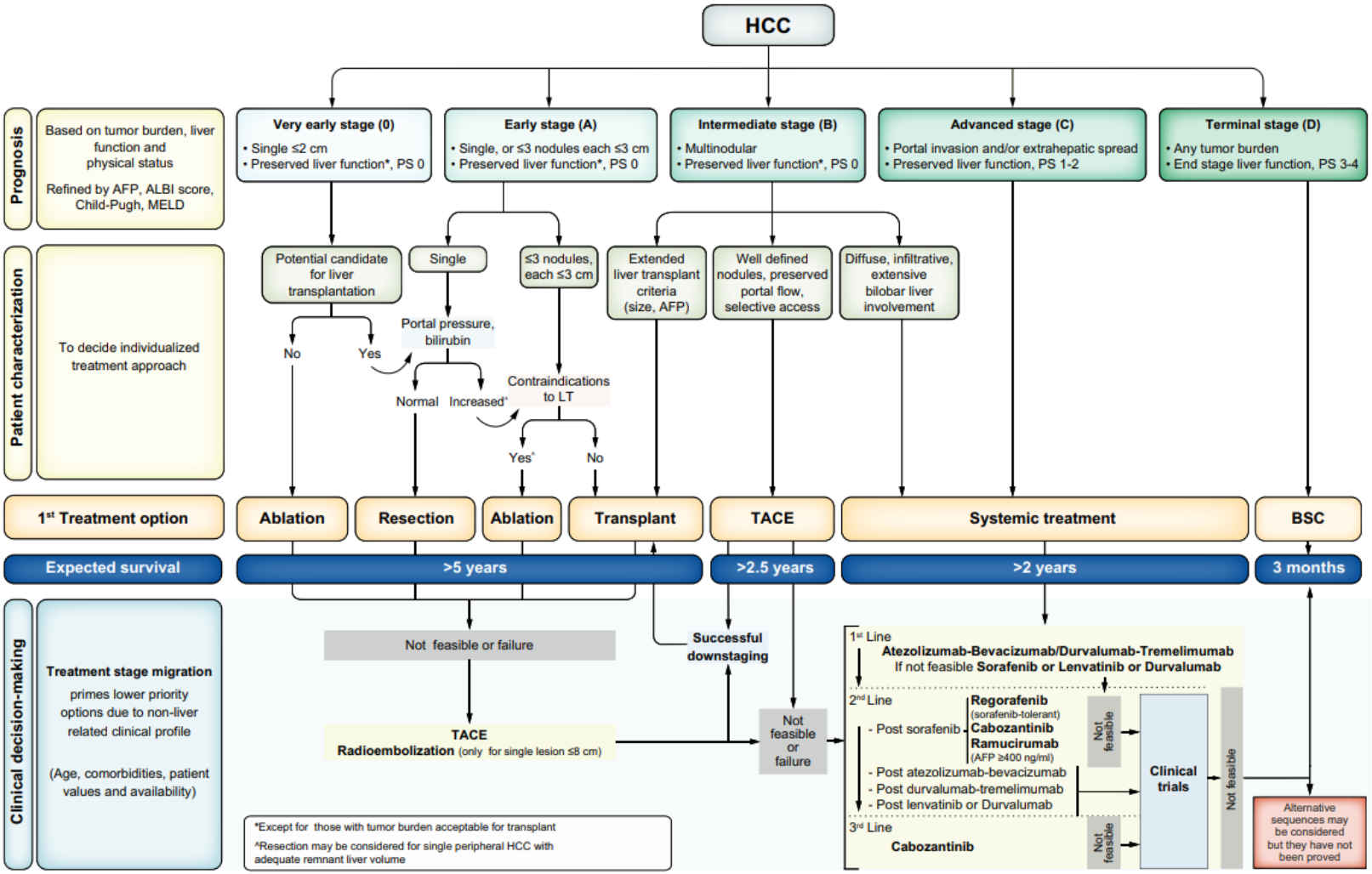


Fig. 1. BCLC staging and treatment strategy in 2022. The BCLC system establishes a prognosis in accordance with the 5 stages that are linked to first-line treatment recommendation. The expected outcome is expressed as median survival of each tumour stage according to the available scientific evidence. Individualised clinical decision-making, according to the available data on November 15, 2021, is defined by teams responsible for integrating all available data with the individual patient's medical profile. Note that liver function should be evaluated beyond the conventional Child-Pugh staging. AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; ECOG-PS, Eastern Cooperative Oncology Group-performance status; LT, liver transplantation; MELD, model of end-stage liver disease; TACE, transarterial chemoembolisation.

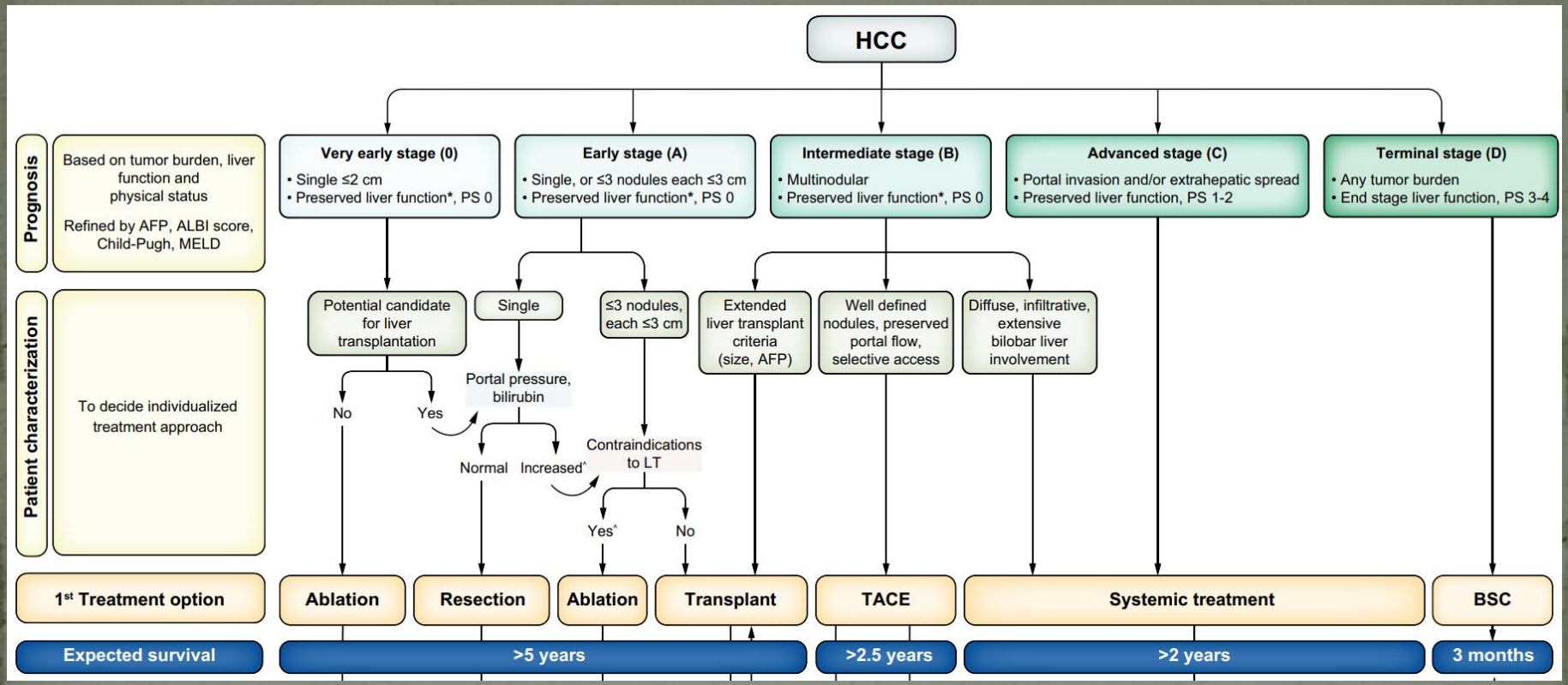

HCC
Prognosis
Based on tumor burden, liver function and physical status
Refined by AFP, ALBI score, Child-Pugh, MELD
Very early stage (0)
• Single ≤2 cm
• Preserved liver function*, PS 0
Early stage (A)
• Single, or ≤3 nodules each ≤3 cm
• Preserved liver function*, PS 0
Intermediate stage (B)
• Multinodular
• 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

TABLE 1. CHILD-PUGH SCORE			
Finding	**1 Point**	**2 Points**	**3 Points**
Encephalopathy grade	None	Mild	Severe
Ascites	Absent	Mild to moderate	Severe, refractory
Total bilirubin (mg/dL)	< 2	2–3	> 3
Serum albumin (g/dL)	> 3.5	2.8–3.5	< 2.8
INR	< 1.7	1.71–2.20	> 2.20

Child-Pugh class A = 5-6 points, class B = 7-9 points, class C = 10-15 points. Abbreviation: INR, international normalized ratio.

Grading of the symptoms of hepatic encephalopathy is performed according to the so-called West Haven classification system[22] :

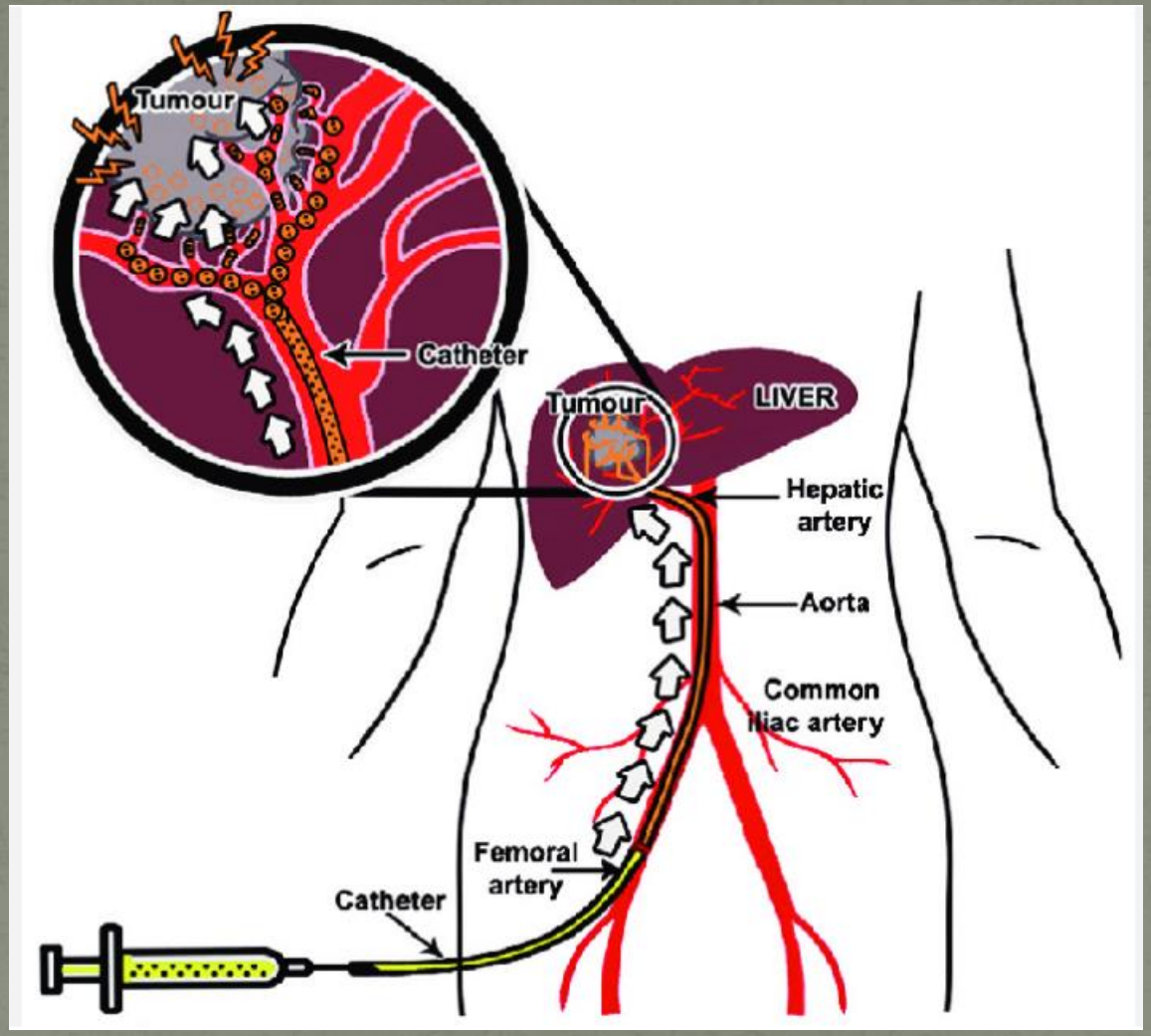
- Grade 0 - Minimal hepatic encephalopathy (also known as covert hepatic encephalopathy [23] and previously known subclinical hepatic encephalopathy); lack of detectable changes in personality or behavior; minimal changes in memory, concentration, intellectual function, and coordination; asterixis is absent.
- Grade 1 - Trivial lack of awareness; shortened attention span; impaired addition or subtraction; hypersomnia, insomnia, or inversion of sleep pattern; euphoria, depression, or irritability; mild confusion; slowing of ability to perform mental tasks
- Grade 2 - Lethargy or apathy; disorientation; inappropriate behavior; slurred speech; obvious asterixis; drowsiness, lethargy, gross deficits in ability to perform mental tasks, obvious personality changes, inappropriate behavior, and intermittent disorientation, usually regarding time
- Grade 3 - Somnolent but can be aroused; unable to perform mental tasks; disorientation about time and place; marked confusion; amnesia; occasional fits of rage; present but incomprehensible speech
- Grade 4 - Coma with or without response to painful stimuli

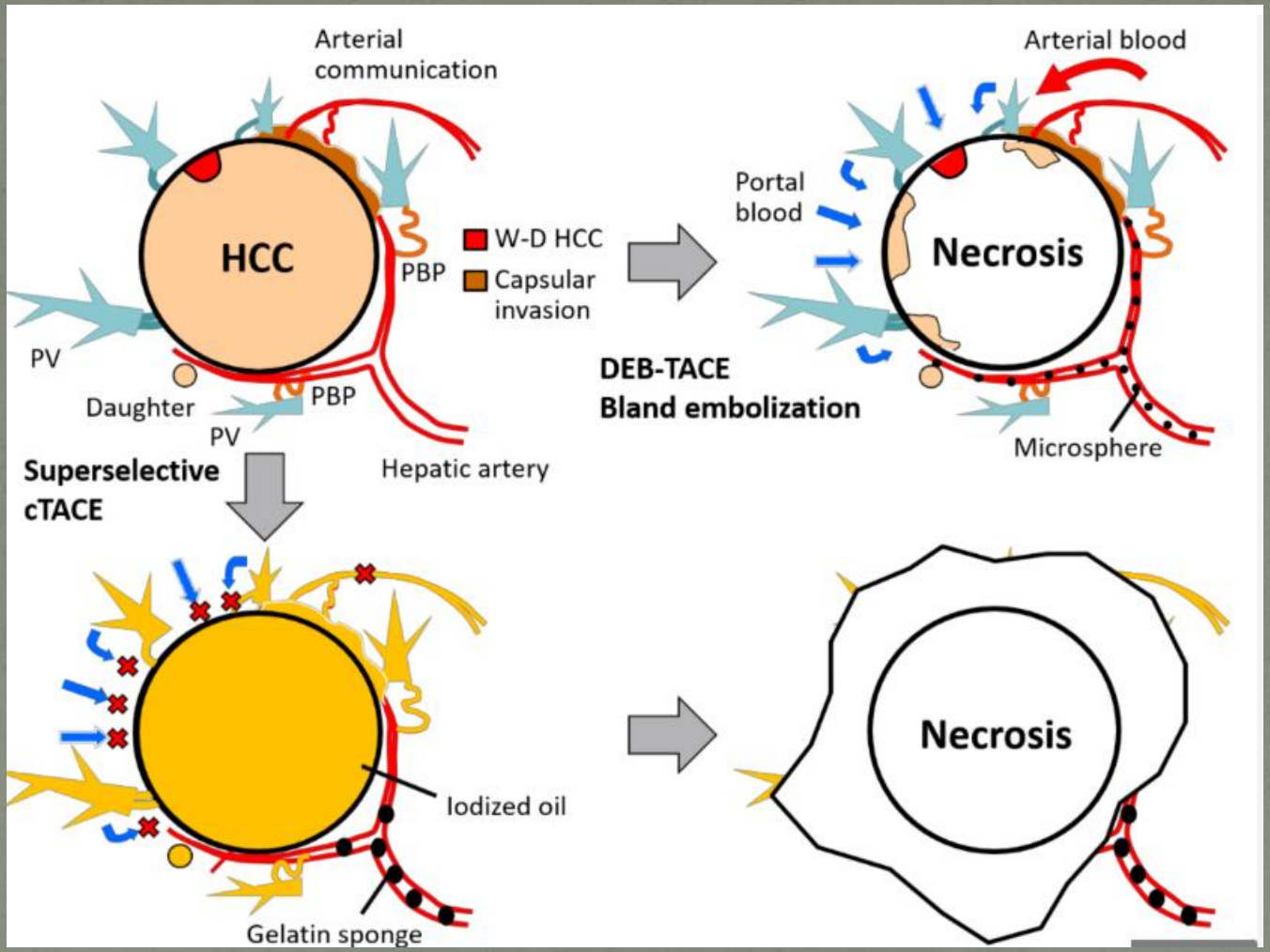
ECOG PS

Eastern Cooperative Oncology Group Performance Status

TABLE 2. ECOG PERFORMANCE STATUS	
Grade	**Description**
0	Fully active, able to carry out all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair
5	Dead

Transarterial Chemoembolization (TACE)


Tumour
Catheter
Tumour
LIVER
Hepatic artery
Aorta
Common iliac artery
Femoral artery
Catheter


Arterial communication
HCC
W-D HCC
Capsular invasion
PBP
PV
Daughter
PBP
PV
Hepatic artery
Superselective cTACE
Arterial blood
Portal blood
Necrosis
DEB-TACE
Bland embolization
Microsphere
Iodized oil
Gelatin sponge
Necrosis

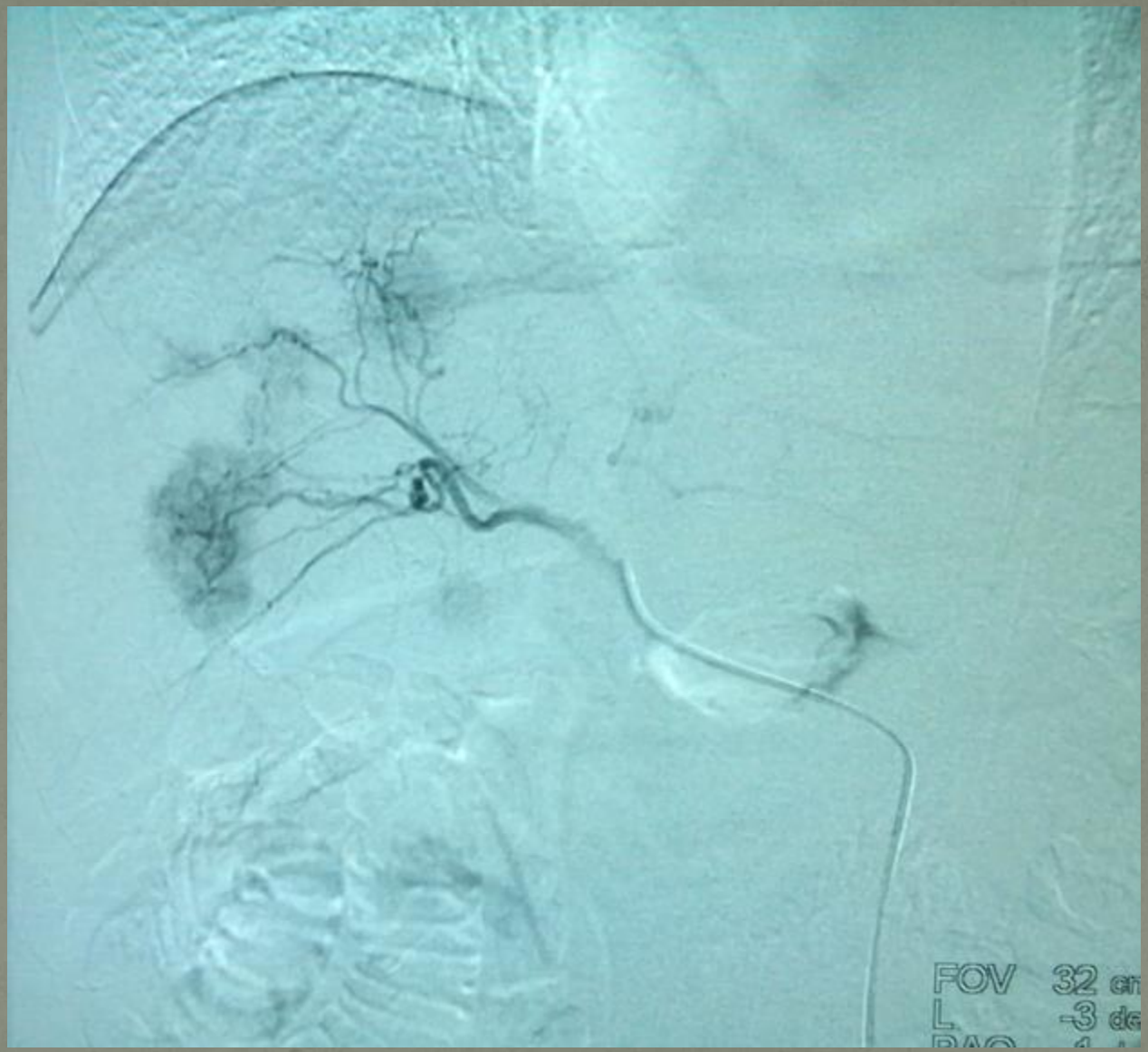
- HCC
- NET
- mCRC
- Cholangiocarcinoma
- Breast cancer mets
- Uveal melanoma mets

TACE indications:

- **palliation of unresectable HCC**
- **as an adjunctive therapy to liver resection**
- **as a bridge to liver transplantation**

Absolute contraindications
Factors related to liver cirrhosis: • Decompensated cirrhosis (Child-Pugh B, score >8), including jaundice, clinical hepatic encephalopathy, and refractory ascites and/or hepatorenal syndrome • Impaired portal-vein blood flow (portal-vein thrombus, hepatofugal blood flow)
Factors related to HCC • Extensive tumour involving the entirety of both lobes of the liver • Malignant portal vein thrombosis
Technical contraindication to hepatic intra-arterial treatment: • e.g., untreatable arteriovenous fistula
Impaired renal function • Creatinine ≥2 mg/dl or creatinine clearance <30 ml/min
Relative contraindications
Factors related to liver cirrhosis: • Untreated oesophageal varices at high risk of bleeding
Factors related to HCC: • Large tumour (>10 cm)
Others factors: • Severe comorbidities • Incompetent papilla with aerobilia (owing to biliary stenting or surgery) • Biliary dilatation

- 1.intra-arterial injection of a mixture of chemotherapeutic agent(s) with ethiodized oil, followed by
- 2.arterial embolization of the tumor feeding vessel(s)


FOV 32 cm
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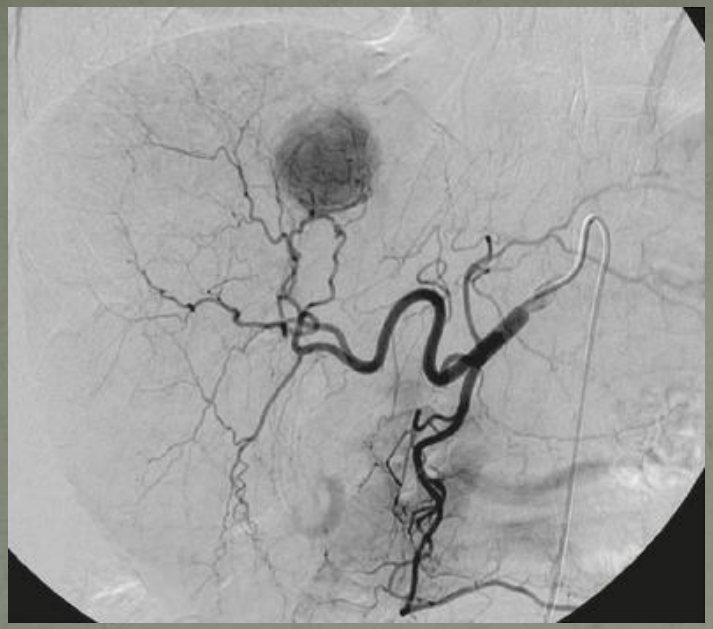
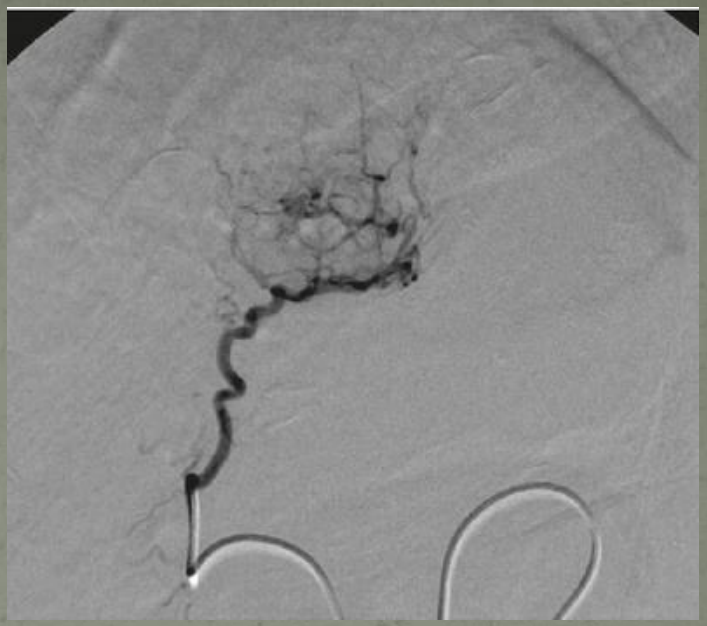
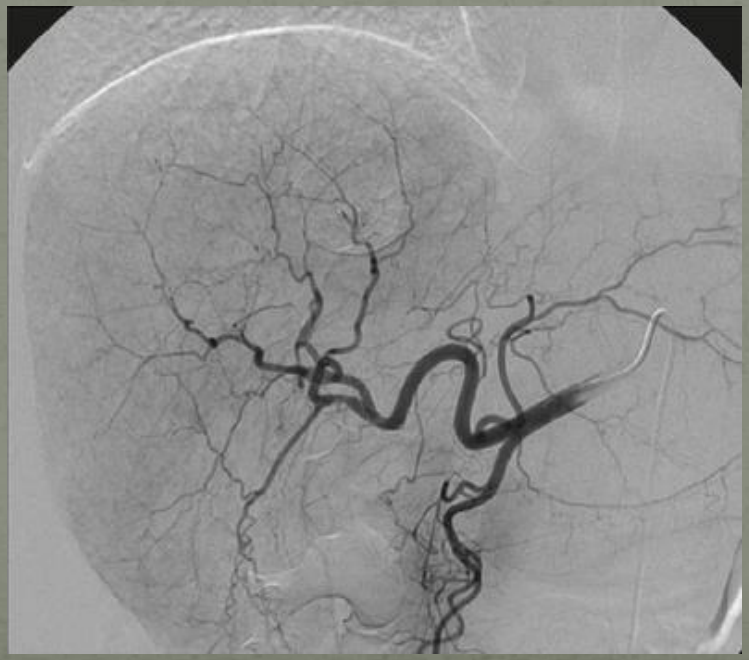
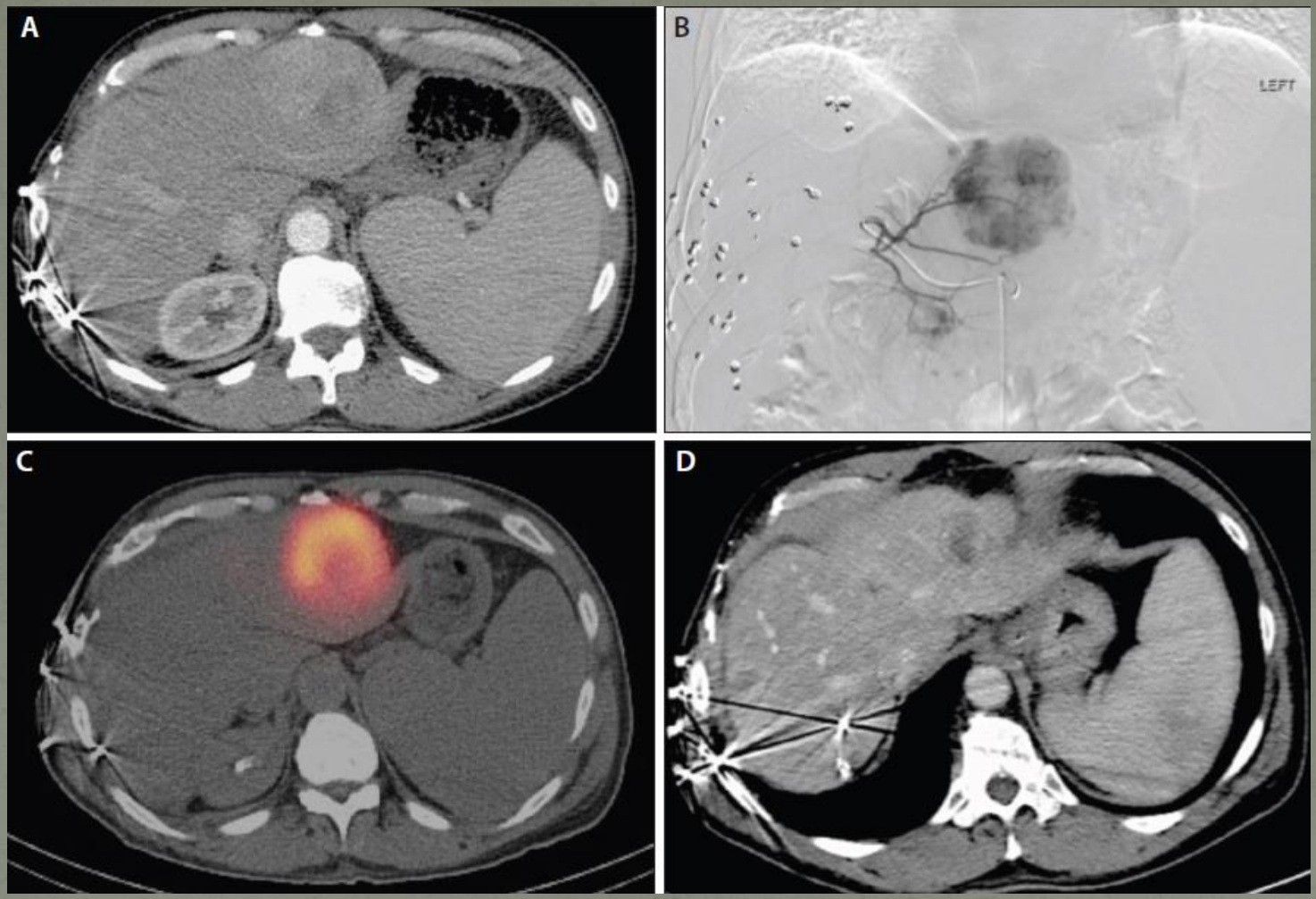
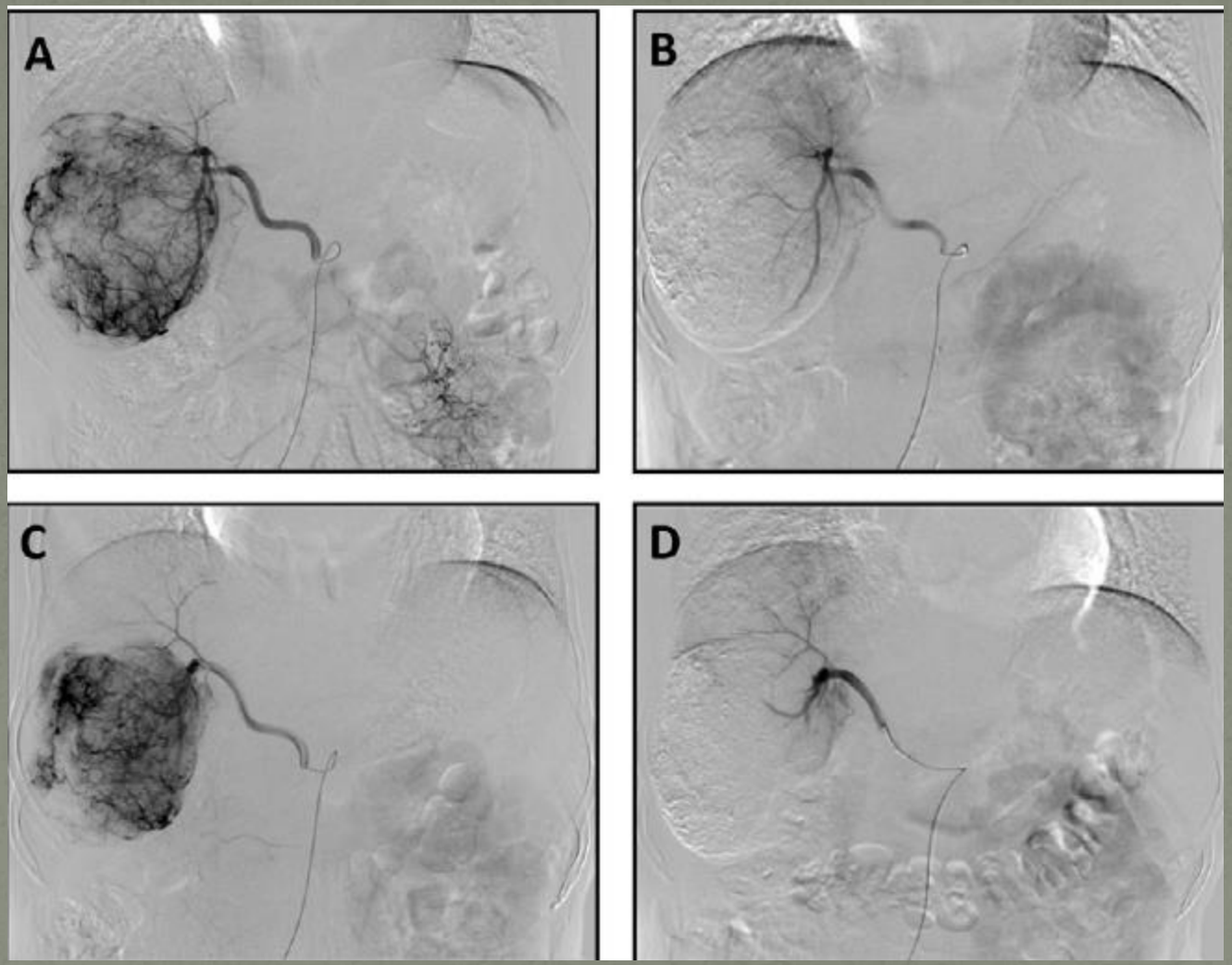







A
B
LEFT
C
D


A
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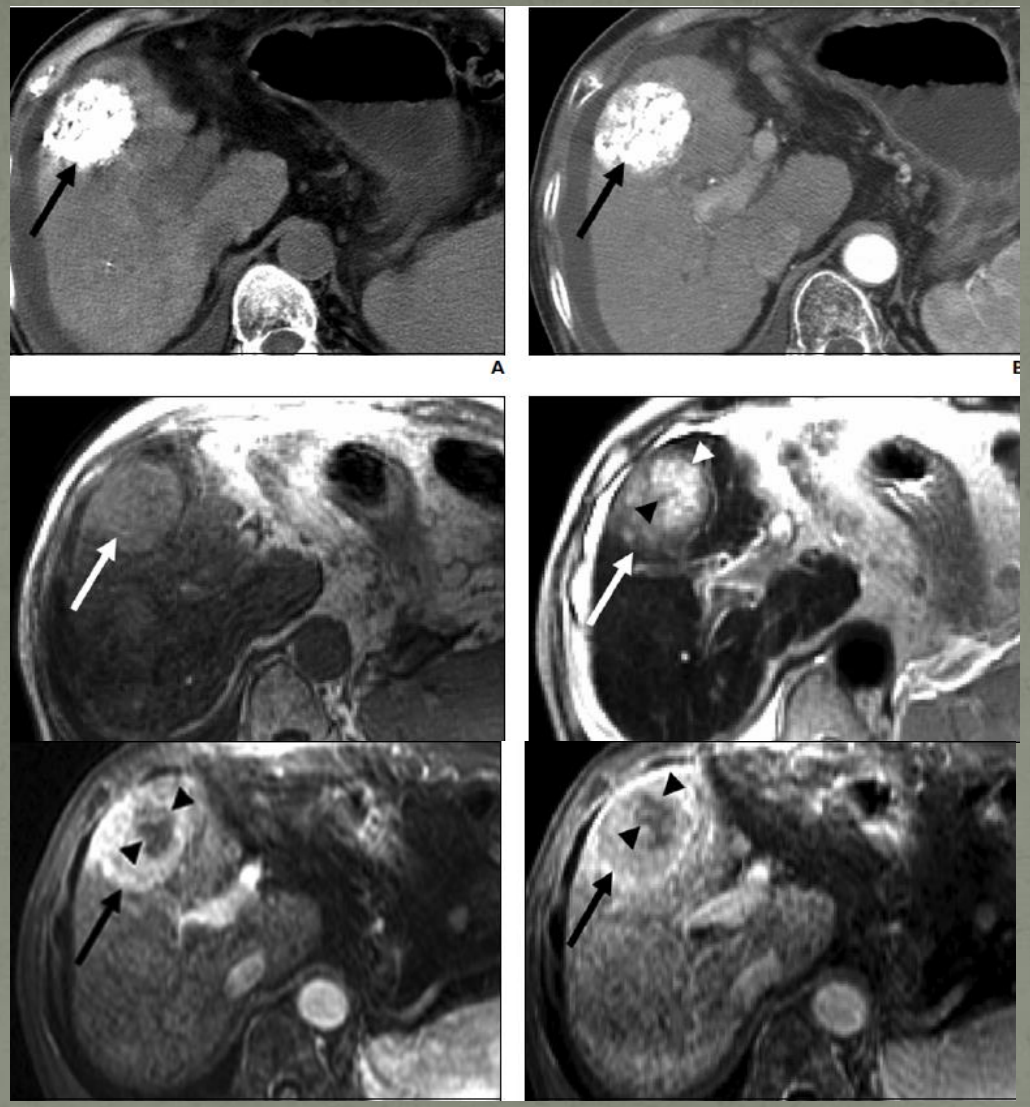

A
B

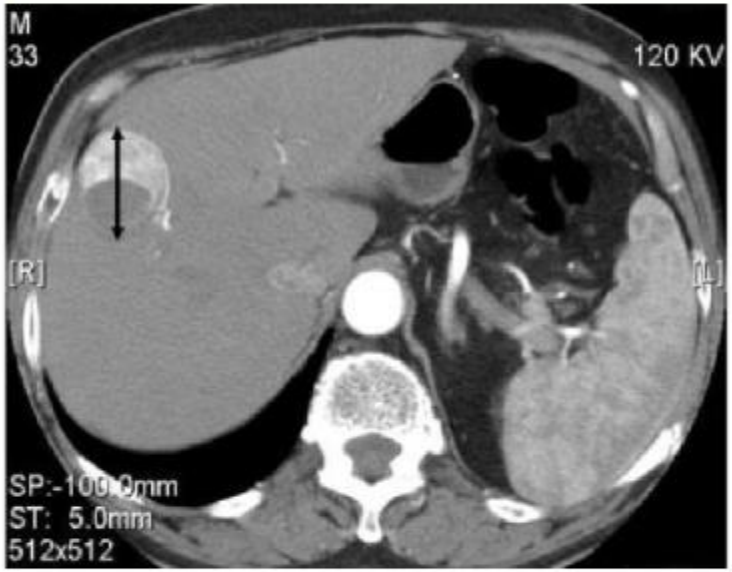
Modified RECIST

- WHO and RECIST criteria do not accurately assess anti-tumor therapies which do not result in tumor shrinkage
- mRECIST recommended by AASLD

Response	WHO	RECIST	mRECIST
Complete Response	Disappearance of all lesions		Disappearance of intratumoral arterial enhancement
Partial Response	>50% decrease	>30% decrease	>30% decrease in viable target lesions
Stable Ds	Neither PR or PD	Neither PR or PD	Neither PR or PD
Progression	> 25% increase	> 20% increase	>20% increase in viable target lesions

Reporting of Post-Treatment Response

Longest Overall Tumor Diameter



Longest Viable Tumor Diameter

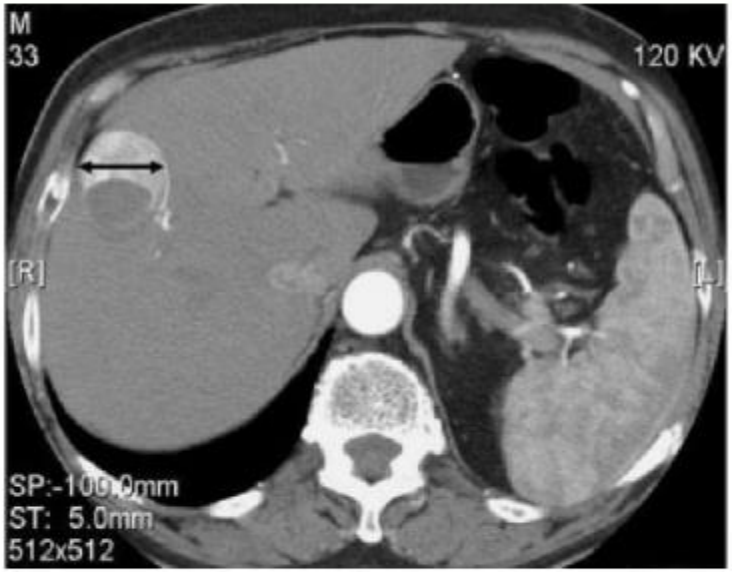
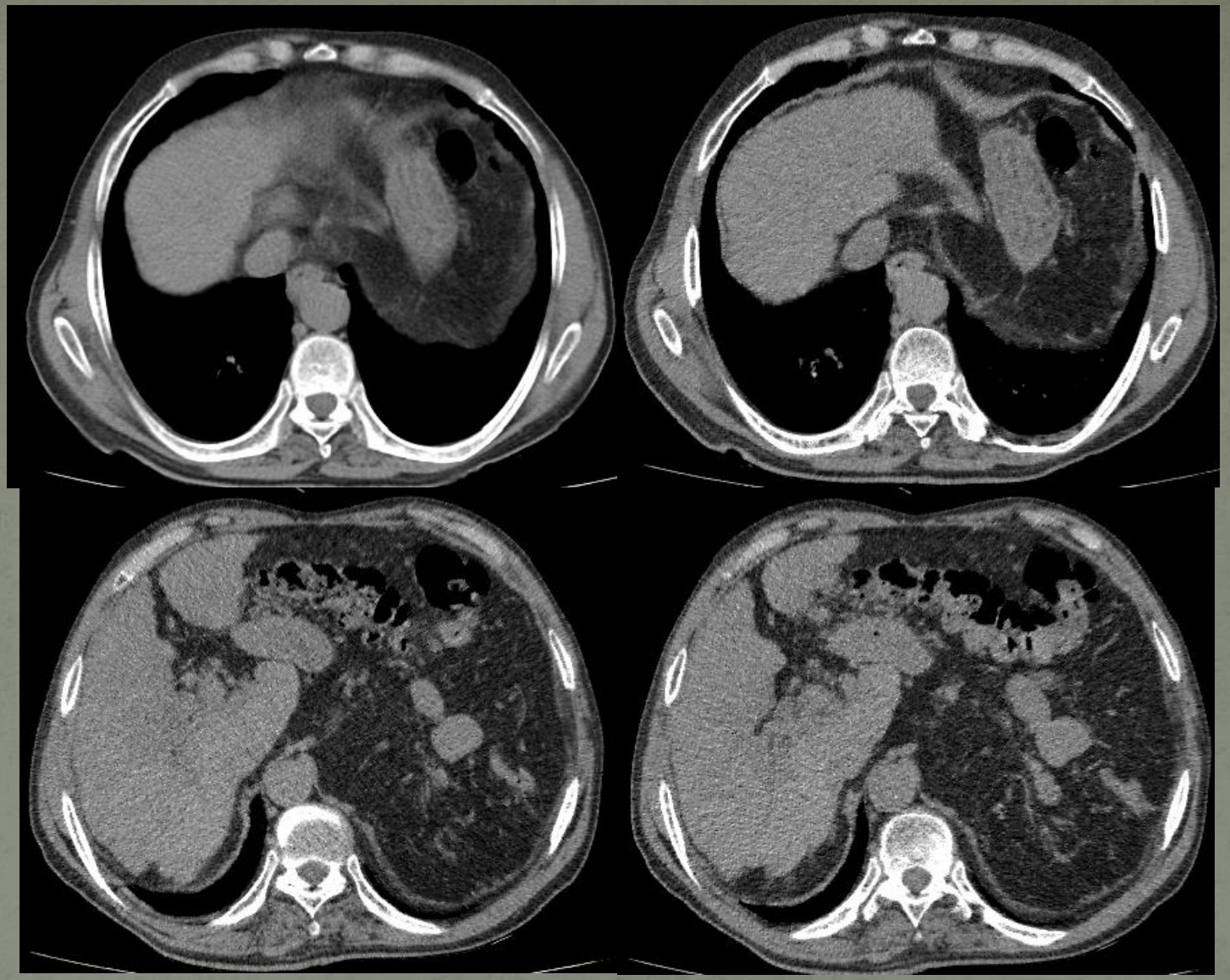


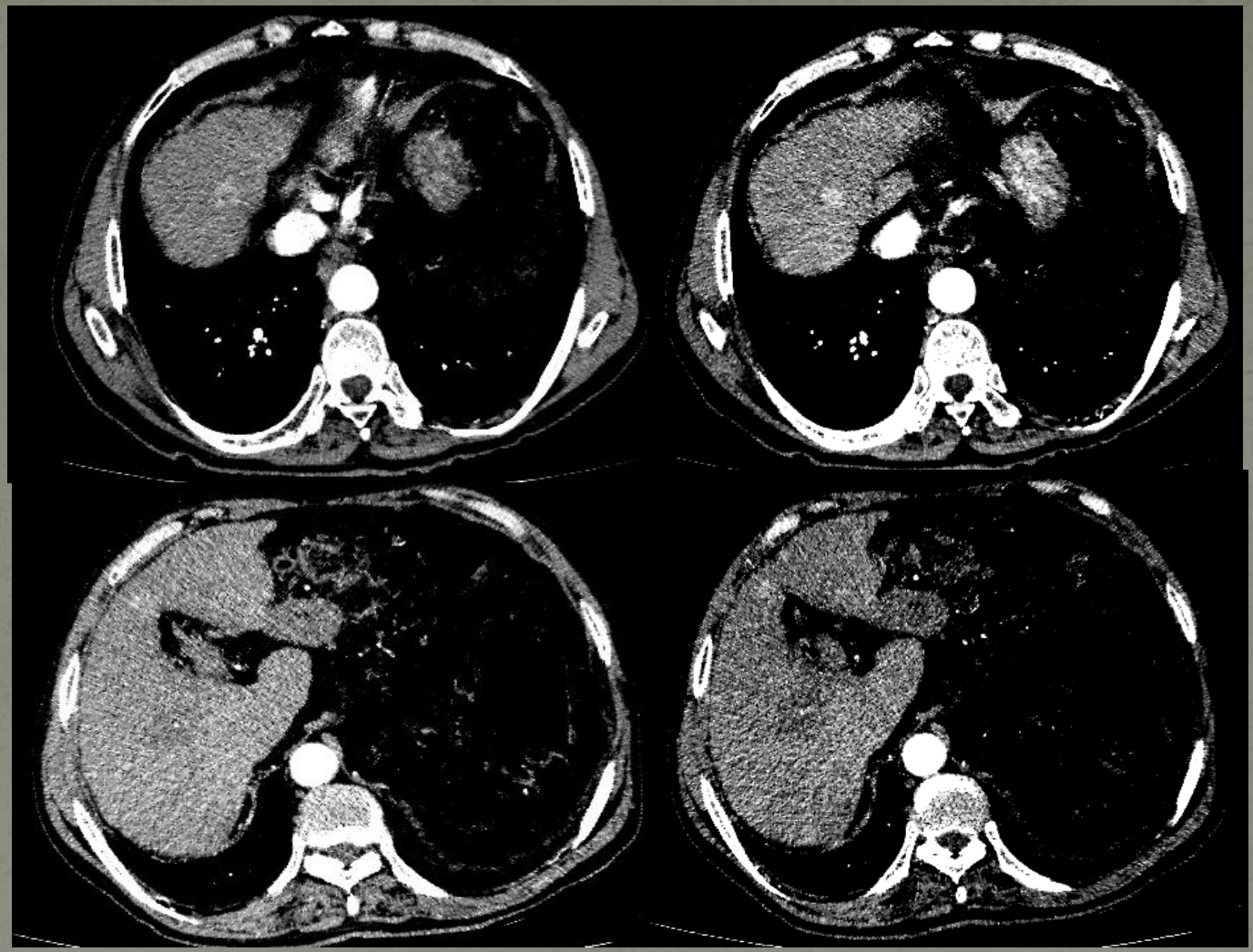
Table 1. ART-score.

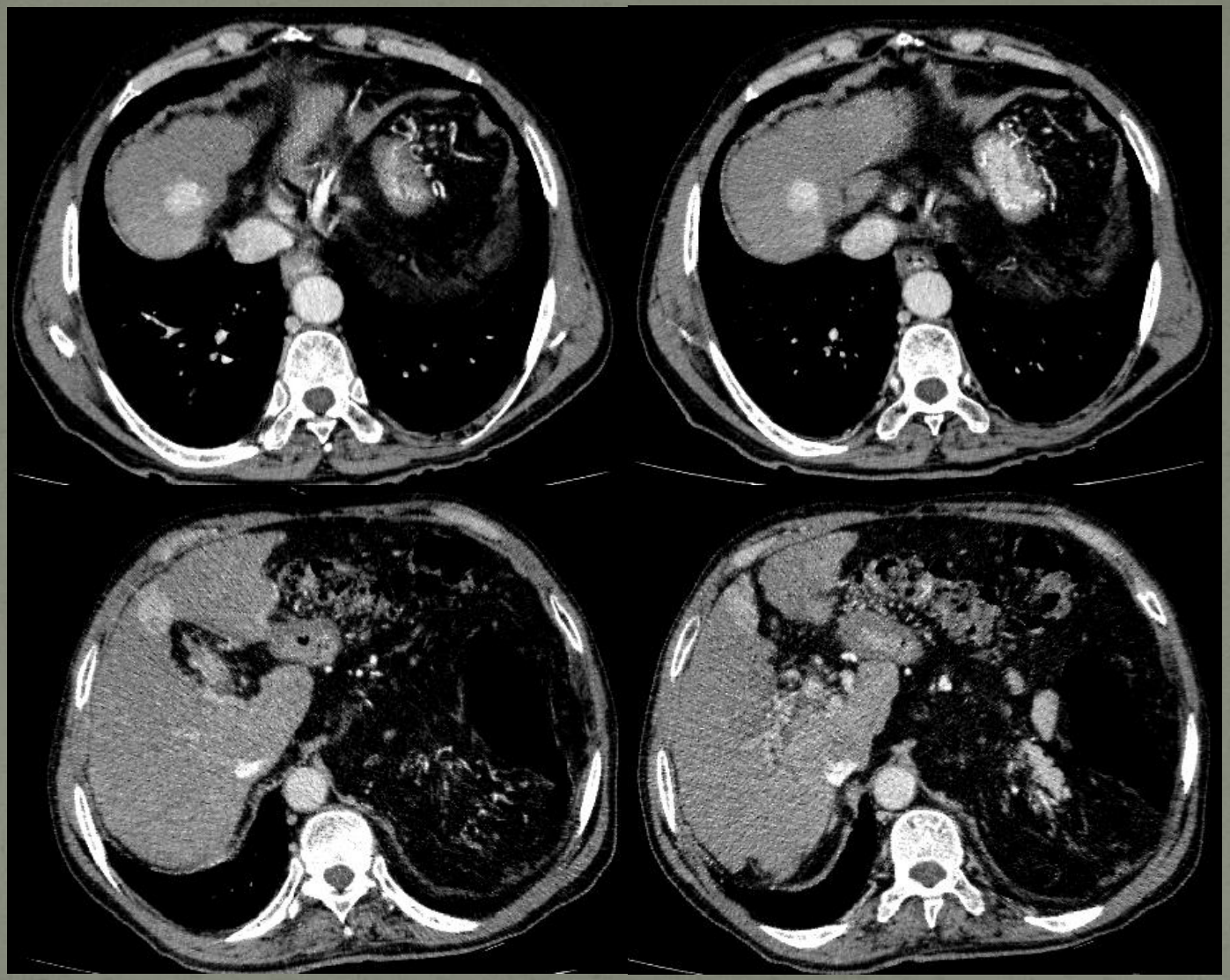
	Points
Radiologic tumor response	
Absent	1
Present	0
AST increase >25%	
Present	4
Absent	0
Child-Pugh score increase	
1 point	1.5
≥2 points	3
Absent	0

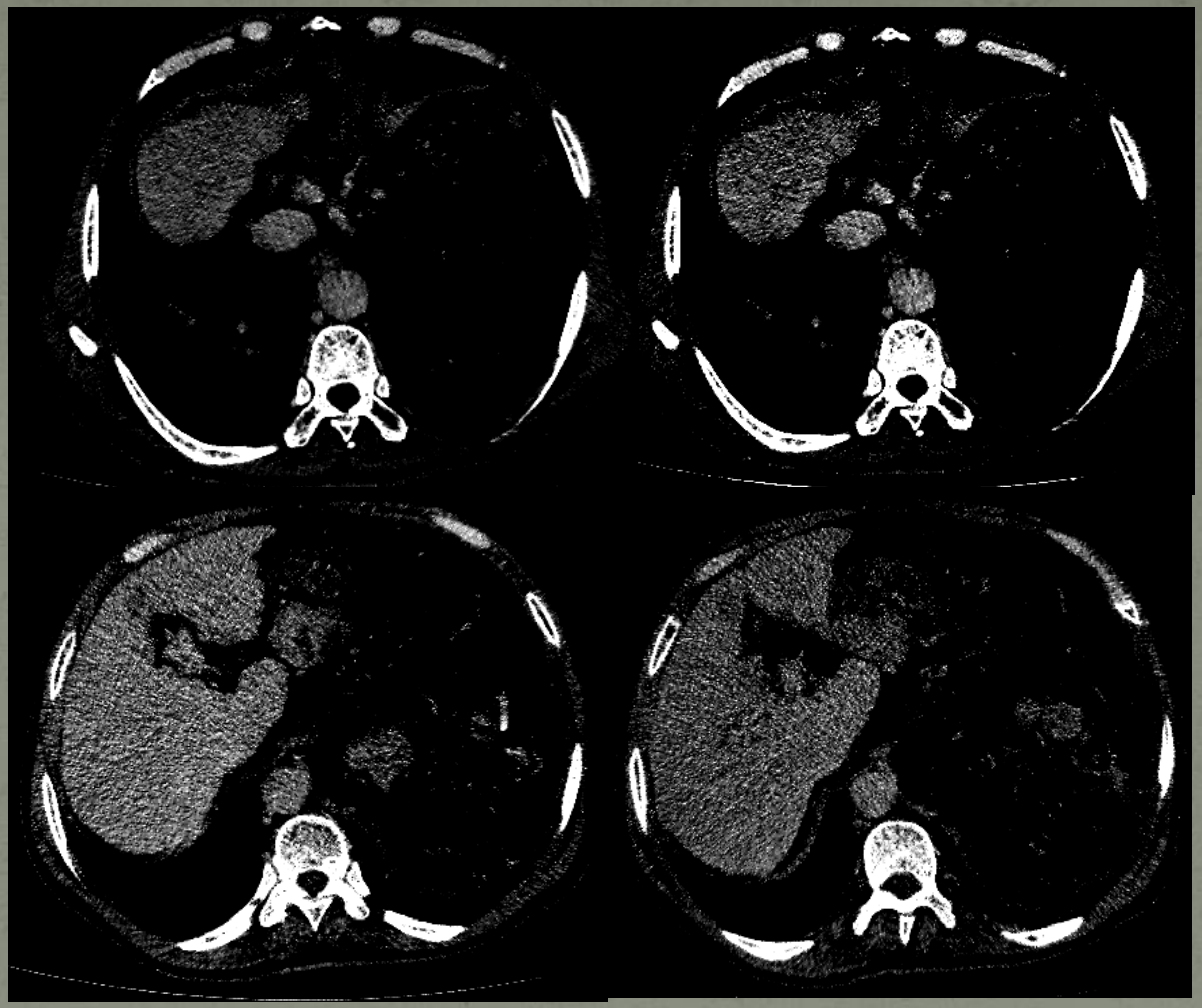
AST, aspartate transaminase.

- A 64 years old man with cirrhosis and elevated AFP









Biochemistry

Test	Result	Unit	Refrence Range
Urea	36	mg/dL	13 - 43
Creatinine	0.97	mg/dL	0.5 - 1.4
Total Bilirubin	1.1	mg/dL	0.1-1.2
Direct Bilirubin	0.4	mg/dL	Up to 0.25
S.G.O.T. (AST)	37	U/L	Up to 40
S.G.P.T. (ALT)	18	IU/L	Up to 42
Alkaline Phosphatase	233	IU/L	80 - 306

Hematology

Test	Result	Unit	Refrence Range
E.S.R 1h	20	mm/h	0 - 30
E.S.R 2h	38	mm/h	
P.T. (Patient)	13.5	Sec	11-13.5
P.T. Activity	81.5	%	100 %
INR	1.1		0.8-1.1
P.T.T.	35	Sec	25 - 40

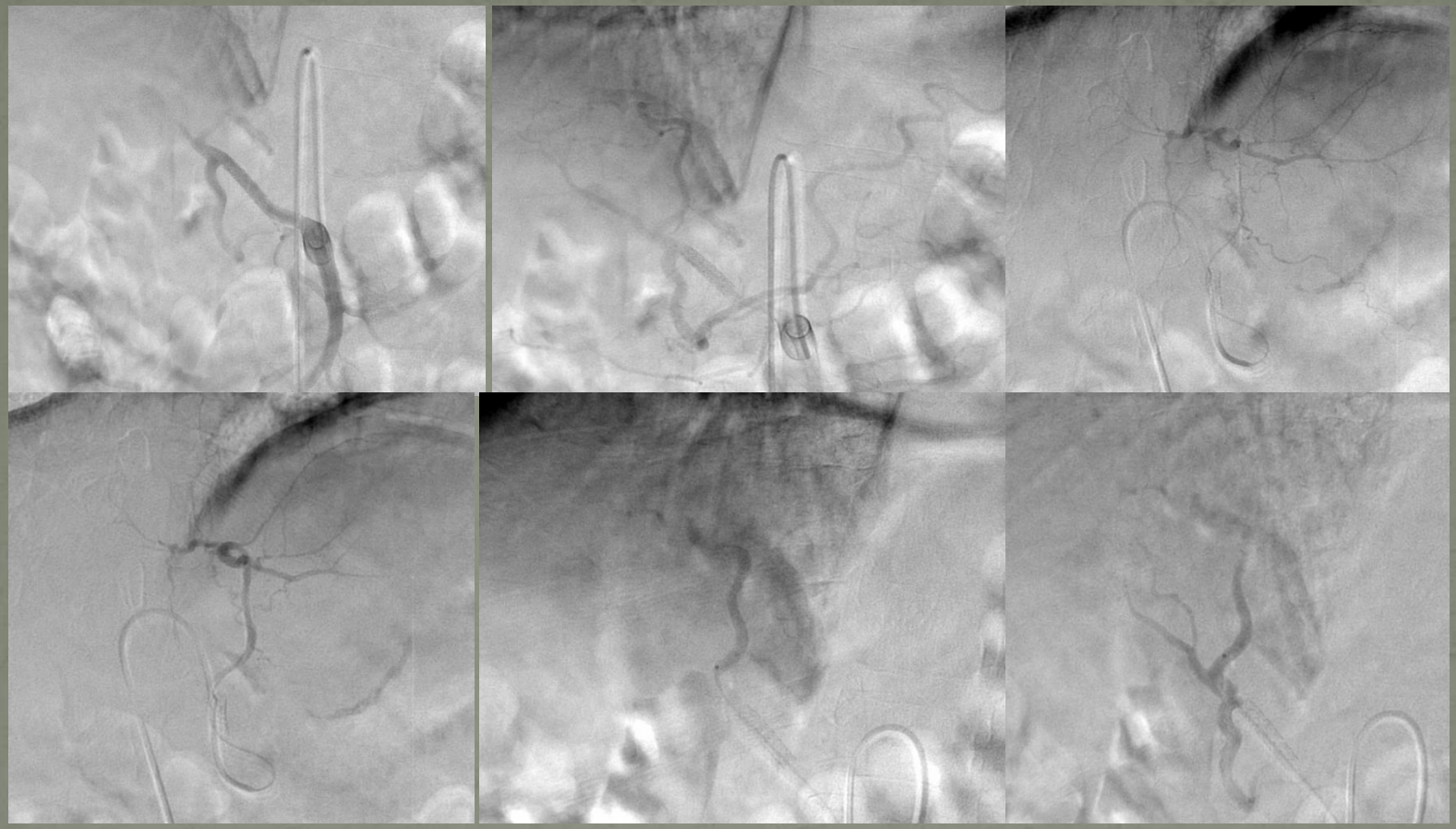
Serology

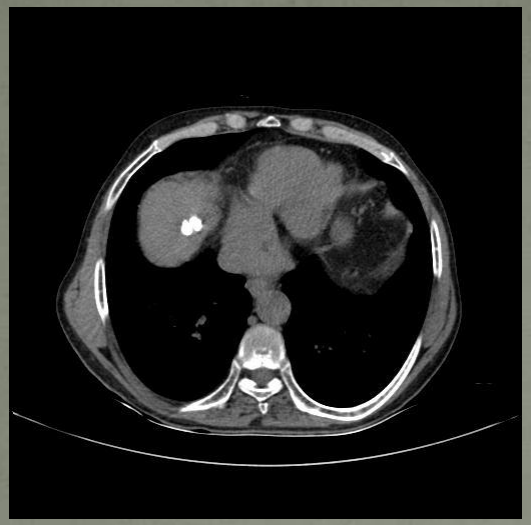
Test	Result	Unit	Refrence Range
CRP	2++		Non reactive

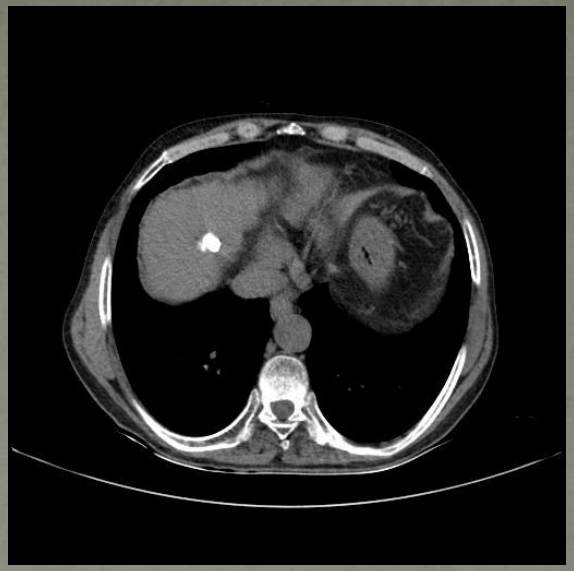
Tumor Markers

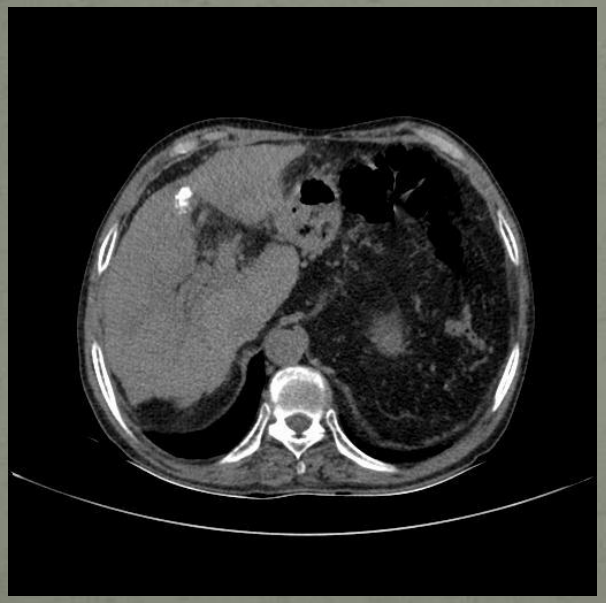
Test	Result	Unit	Refrence Range
Alpha Feto Protein	♦ 111	ng/ml	Up to 7

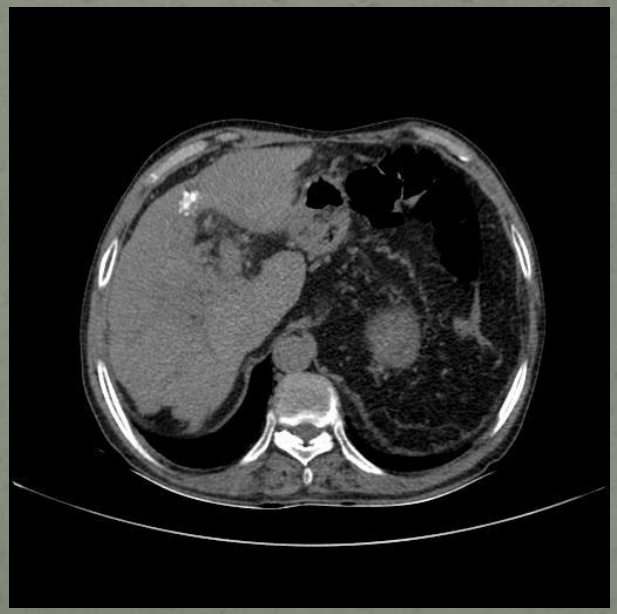
Normal ranges are according to the patients sex and age.

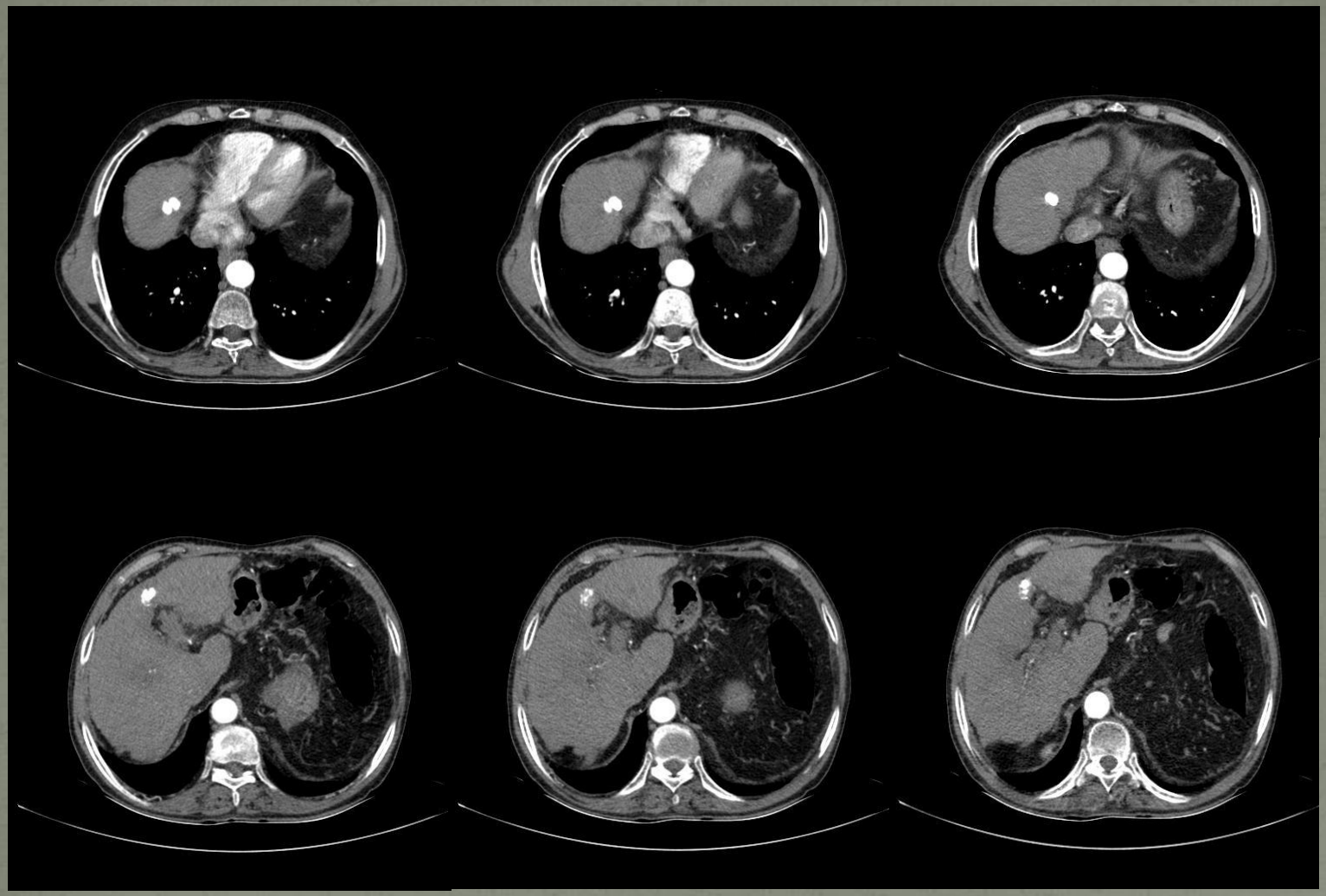


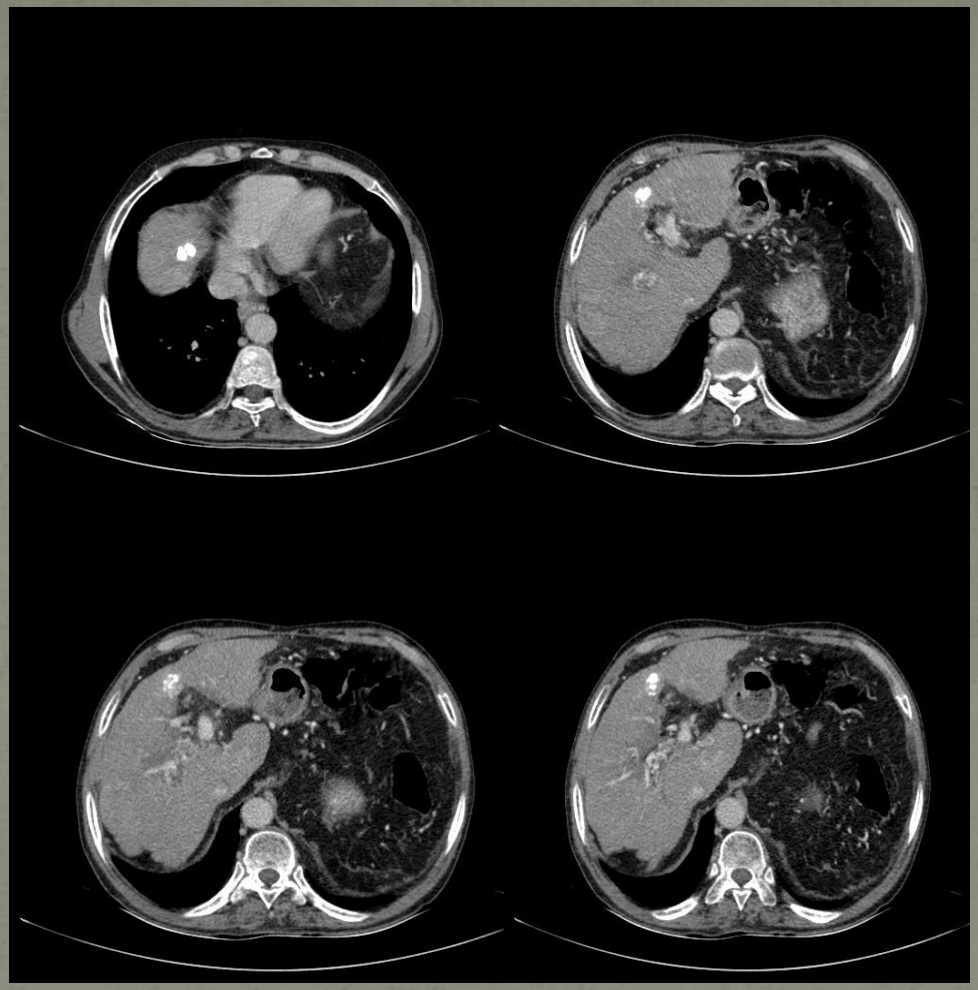


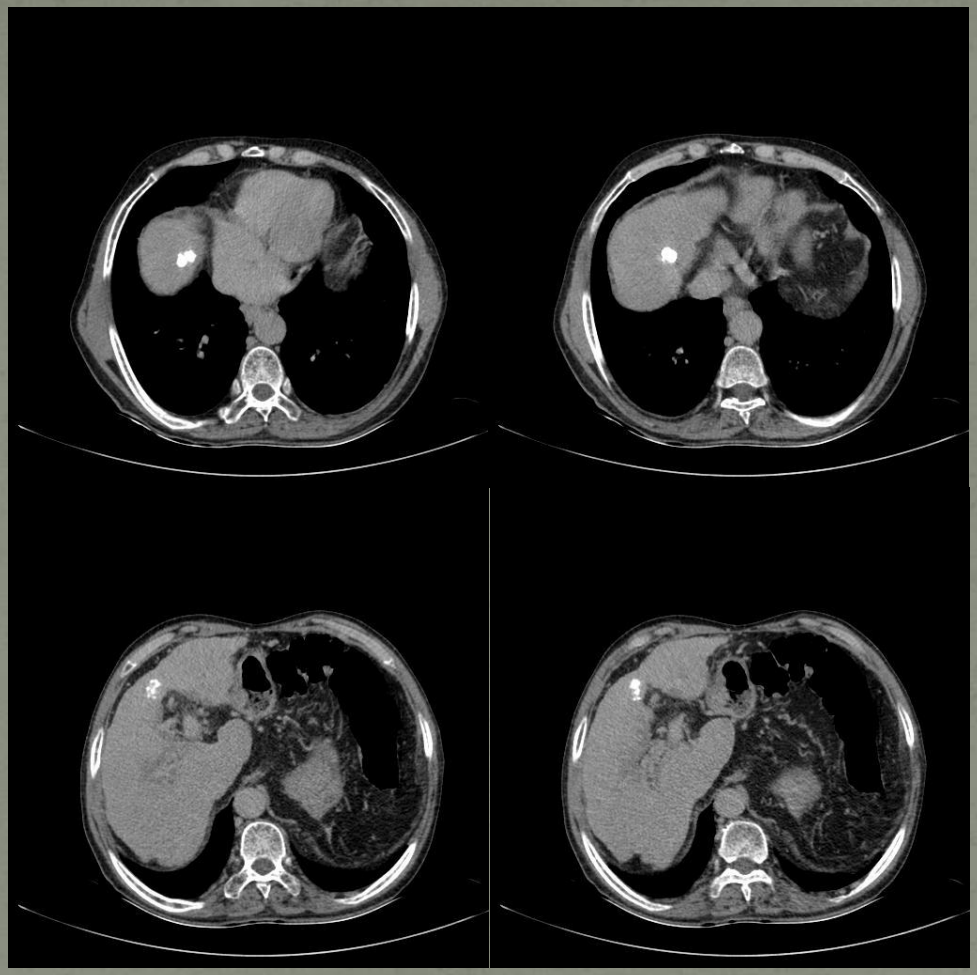












Biochemistry

Test	Result	Unit	Refrence Range
Urea	23	mg/dL	13 - 43
Creatinine	1.18	mg/dL	0.5 - 1.4
Total Bilirubin	0.73	mg/dL	0.1-1.2
Direct Bilirubin	0.32	mg/dL	Up to 0.25
S.G.O.T. (AST)	▲ 42	U/L	Up to 40
S.G.P.T. (ALT)	25	IU/L	Up to 42
Alkaline Phosphatase	▲ 311	IU/L	80 - 306
Albumin	▼ 3	g/dL	3.5 - 5.2

Hematology

Test	Result	Unit	Refrence Range
E.S.R 1h	▲ 61	mm/h	0 - 30
E.S.R 2h	81	mm/h	
P.T. (Patient)	14.9*	Sec	11-13.5
P.T. Activity	65.7	%	100 %
INR	▲1.3		0.8-1.1
Control PT	13		
P.T.T.	45	Sec	25 - 45

* = Confirmed by Repeated Analysis

Serology

Test	Result	Unit	Refrence Range
CRP	Positive(2+)		Non reactive

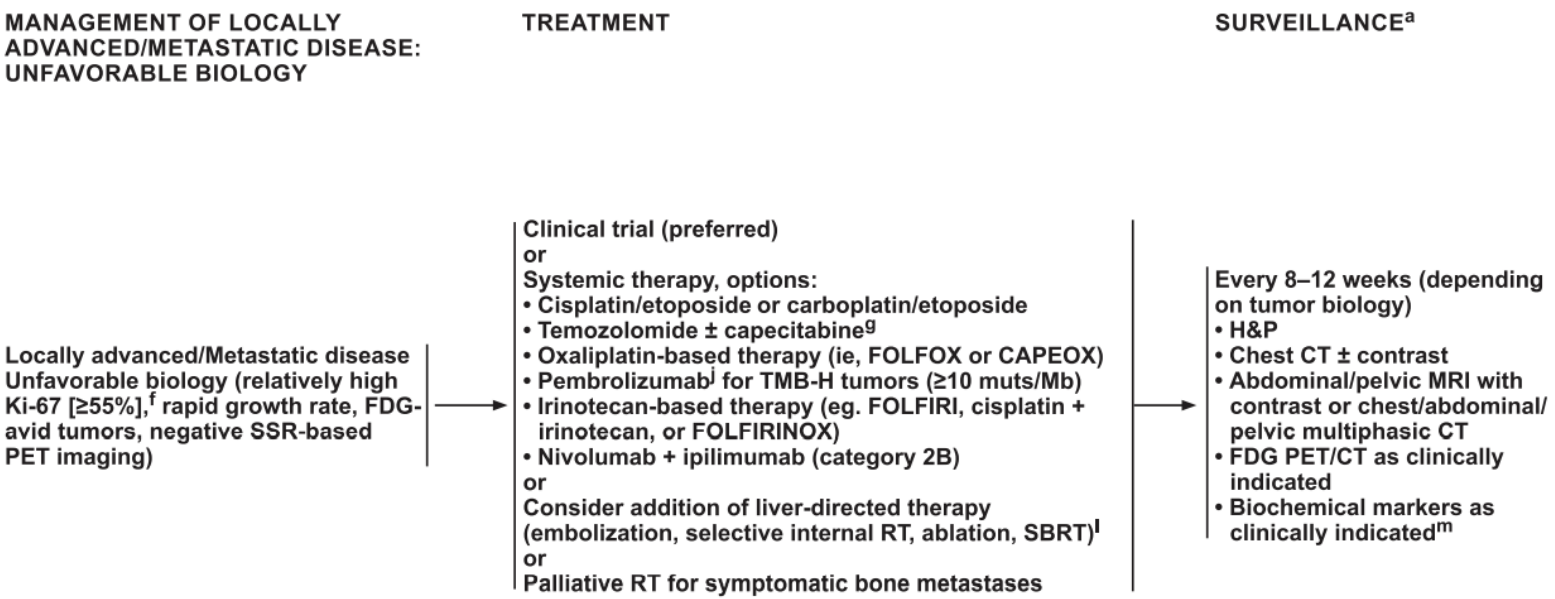
Tumor Markers

Test	Result	Unit	Refrence Range
Alpha Feto Protein	▲ 12.2	ng/ml	Up to 7

Normal ranges are according to the patients sex and age.

- Chemoembolization is also indicated in some non-resectable patients. Use of drug eluting beads, TACE with irinotecan (DEBIRI), is indicated as a third-line treatment when systemic chemotherapy has failed
- Selective intraarterial administration of irinotecan inside tumoral arteries, while the embolization limits drug washout, permits a higher and prolonged intratumoral dose of irinotecan and up to 70–75% lower plasma levels Current evidence for DEBIRI is mostly limited to the salvage setting. Two randomized controlled trials demonstrated an improved objective response rate (ORR) compared with FOLFOX and FOLFIRI
- DEBIRI could provide an opportunity for some patients who need downstaging prior to surgery

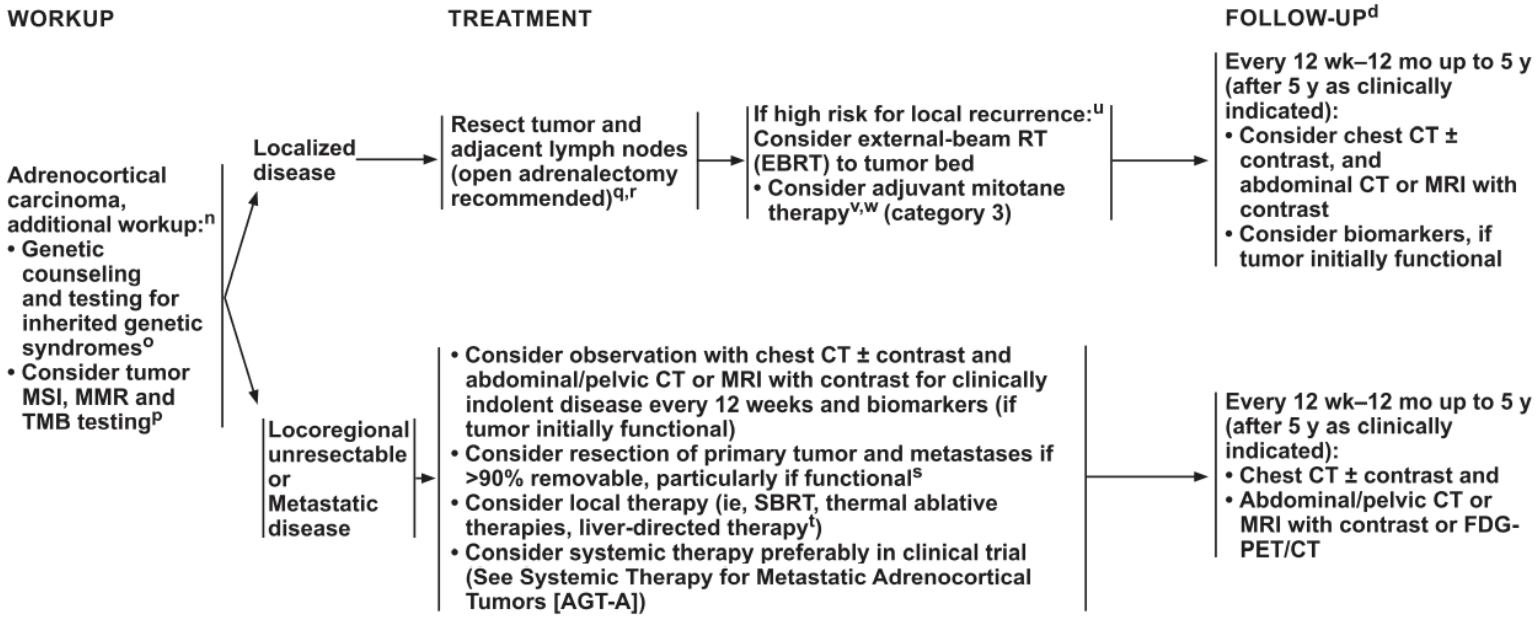
Well-Differentiated, Grade 3 Neuroendocrine Tumors



[a] See Principles of Imaging (NE-B*).
[f] There are limitations in terms of the data for what the appropriate cutoff should be, as well as variability/heterogeneity of Ki-67 in a given tumor and over time in serial biopsies. The clinical course and histopathologic workup combined should dictate therapy, not solely Ki-67.
[g] May have more activity in tumors arising in pancreas and with.
[j] Pembrolizumab is an option for patients with advanced tumor mutational burden-high (TMB-H) tumors (as determined by an FDA-approved test) that have progressed following prior treatment and have no satisfactory alternative treatment options.
[l] Consider liver-directed therapy in selected cases with residual liver-predominant disease after systemic therapy. See Principles of Liver-Directed Therapy for Neuroendocrine Tumor Metastases (NE-H*).
[m] See Principle of Biochemical Testing (NE-C*).

*Available online, in these guidelines, at NCCN.org.

Adrenal Gland Tumors



[d] See Principles of Imaging (NE-B*).
[n] Staging workup, see AGT-4.
[o] See Principles of Genetic Risk Assessment and Counseling (NE-E).
[p] FDA-approved test recommended for determination of TMB.
[q] May require removal of adjacent structures (ie, liver, kidney, pancreas, spleen, diaphragm) for complete resection.
[r] It is important to achieve negative margins and avoid breaching the tumor capsule. There may be an increased risk for local recurrence and peritoneal spread when done with a minimally invasive approach.
[s] If bulky disease, or <90% is removable, surgery can be reconsidered following response to systemic therapy.
[t] See Principles of Liver-Directed Therapy for Neuroendocrine Tumor Metastases (NE-H*).
[u] High-risk local recurrence features include: positive margins, Ki-67 >10%, rupture of capsule, large size, and high grade.
[v] Monitor mitotane blood levels. Some institutions recommend target levels of 14–20 mcg/mL if tolerated. Steady-state levels may be reached several months after initiation of mitotane. Life-long hydrocortisone replacement may be required with mitotane.
[w] Mitotane may have more benefit for control of hormone symptoms than control of tumor.

*Available online, in these guidelines, at NCCN.org.

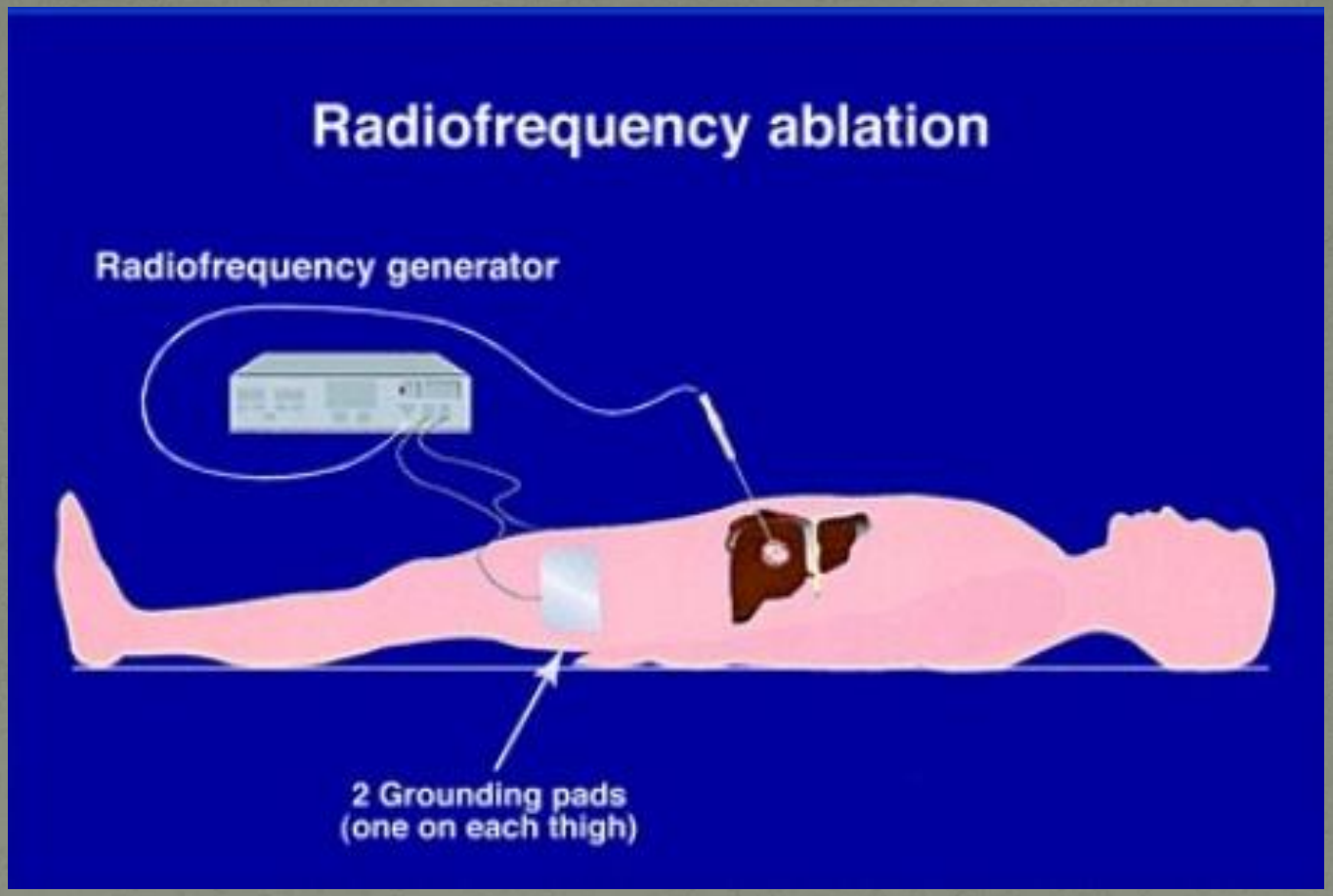
NCCN guideline 2022

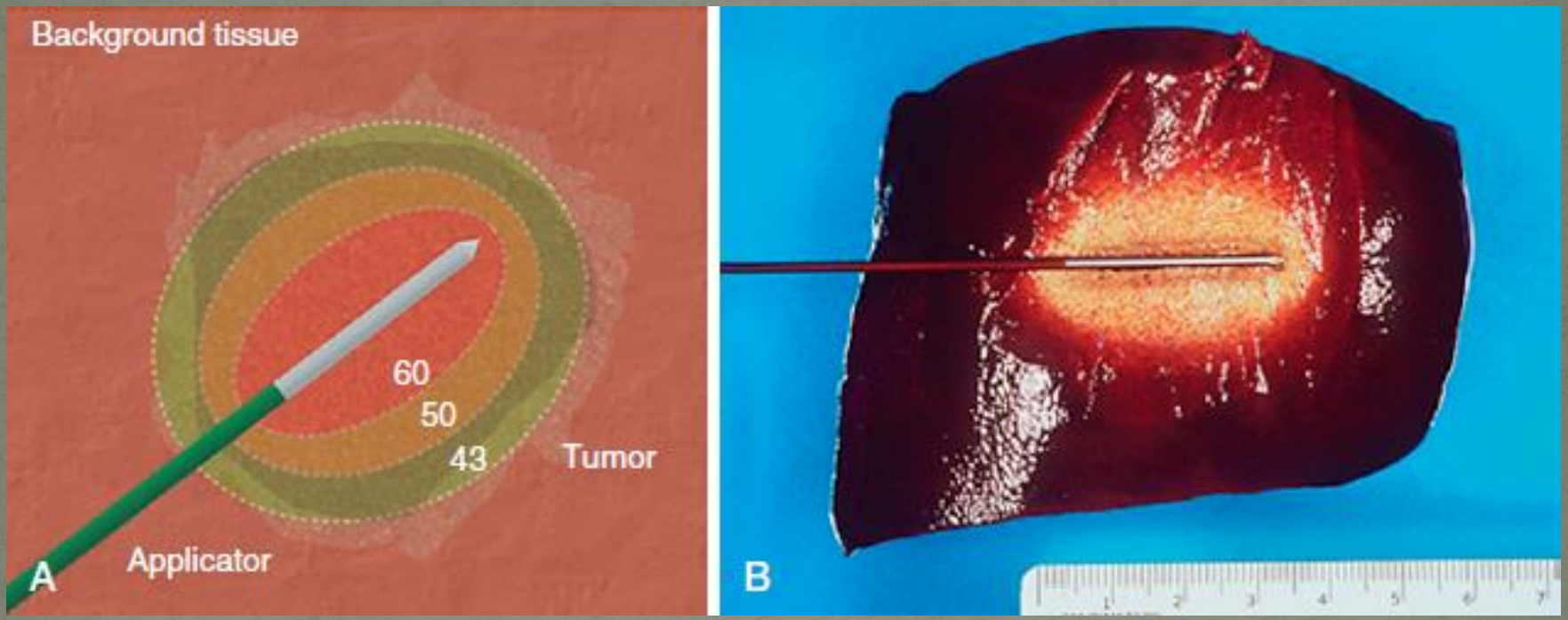
- Local Therapies for Metastases
- The standard of care for patients with resectable metastatic disease is surgical resection. Image-guided ablation has historically been used for non-surgical patients but is also indicated for small metastases that can be treated with margins, in combination with surgery or alone, as long as all visible disease is treated. SBRT is a reasonable option for patients who cannot be resected or ablated, as discussed in subsequent paragraphs. Many patients, however, are not surgical candidates and/or have disease that cannot be ablated with clear margins or safely treated by SBRT. In select patients with liver-only or liver-dominant metastatic disease that cannot be resected or ablated, other local, arterially directed treatment options may be offered

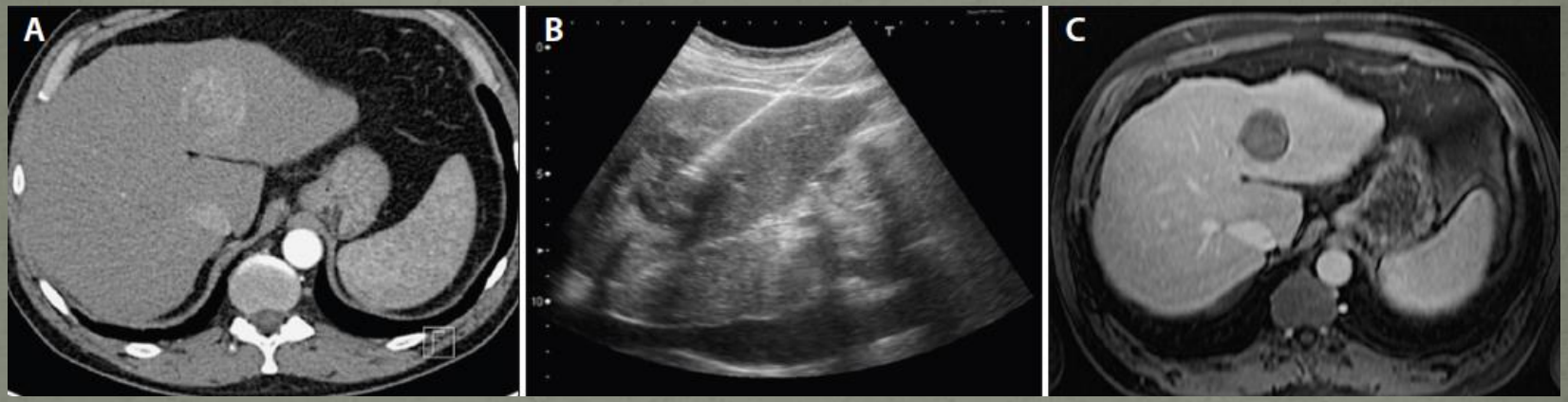
- National Comprehensive Cancer Network (NCCN) and European Society of Medical Oncology (ESMO) guidelines establish a role of vascular-based therapies in patients with liver-dominant metastases who failed systemic chemotherapy

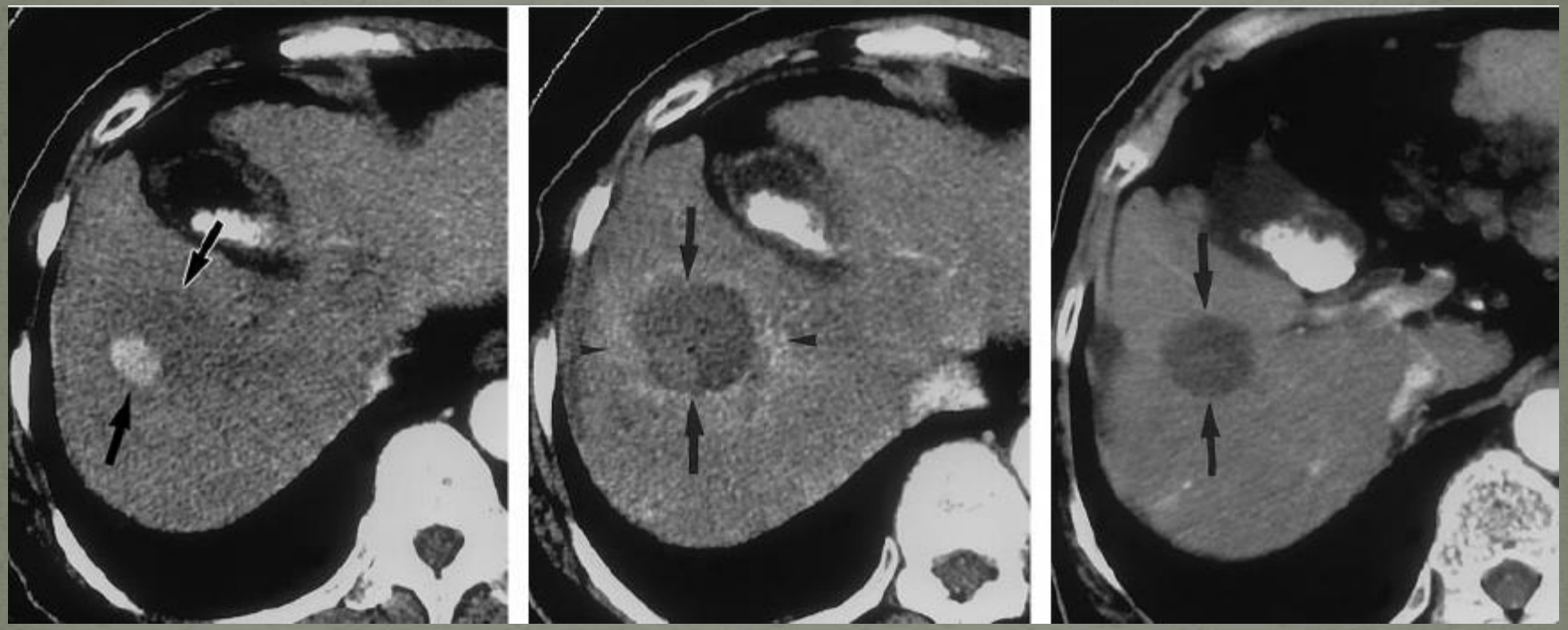
- ESMO guideline 2022
- The data on TACE for CRLMs are mostly related to irinotecan-based drug-eluting microspheres (DEBIRI), including two randomized studies. Despite significant limitations in design and analysis of both, DEBIRI compared with leucovorin–5-FU–irinotecan (FOLFIRI) resulted in statistically significant improved OS and PFS
- whereas FOLFOX–bevacizumab–DEBIRI (FOLFOX-DEBIRI) reported improved response rate (RR), downsizing to resection and PFS compared with FOLFOX–bevacizumab

- Thermal ablation
- 1.Radiofrequency
- 2.Microwave


Radiofrequency ablation
Radiofrequency generator
2 Grounding pads
(one on each thigh)


Background tissue
60
50
43
Tumor
A
Applicator
B


A
B
C



- Tumor Ablation
- Resection is the standard approach for the local treatment of resectable metastatic disease. However, patients with liver or lung oligometastases can also be considered for tumor ablation therapy, particularly in cases that may not be optimal for resection. Ablative techniques include radiofrequency ablation (RFA,microwave ablation (MWA), cryoablation, and electro-coagulation (irreversible electroporation). There is extensive evidence on the use of RFA as a reasonable treatment option for non-surgical candidates and for recurrent disease after hepatectomy with small liver metastases that can be treated with clear margins

- Although resection, when possible, remains the standard of care for CRC liver metastases, ablation with or without resection can offer improved overall survival compared with chemotherapy alone. The CLOCC trial provides level 1 evidence in support of this approach. The NCCN holds this as a category 2A recommendation if all original sites of disease are targeted

- Locoregional treatment also plays a role in non-resectable patients
- Recently, the CLOCC trial has marked a shift in the paradigm of percutaneous ablation in metastatic CRC. The goal is not necessarily to cure the patient. According to this study, radiofrequency or microwave ablation is not limited to patients with resectable tumors and may not be limited by the size of the metastatic nodule. After 7, 8 years of follow-up, in patients with advanced disease who obtained a reduction of the tumoral load by applying additional aggressive treatment consisting of local ablation plus systemic treatment, a benefcial efect was demonstrated clinically and was associated with a statistically signifcant improvement in overall survival