HCC – new frontiers in treatment

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Overview

- Epidemiology
- Etiology
- Clinical presentation
- Diagnosis
- Treatment
- Prognosis

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- Etiology
- Clinical presentation
- Diagnosis
- Treatment
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Introduction

- Most common primary hepatic malignancy
- Annual incidence is 782000 people annually*
- Globally accounts for 9.2% of all new cancer cases
- 5th most common cancer in males and 8th in females
- Around 84% occur in less developed regions
- Annual mortality is 746000*
- Worldwide it is the second leading cause of cancer-related death

*IARC. *Liver Cancer: Estimated Incidence, Mortality, Prevalence Worldwide in* 2012. http://globocaniarcfr/Pages/fact_sheets_canceraspx. 2012. Accessed December 12, 2013.

HCC in Africa

- High prevalence in all Sub-Saharan African countries
- Most common cause of cancer-related death in men and the 3rd most common in women
- Annual fatality ratio is 0.96
- Occurs at a younger age
- A large percentage present in non-cirrhotic livers
- Present with larger tumours
- Present more often metastatic disease

Etiology

- Chronic hepatitis B infection
- Chronic hepatitis C infection
- Dietary aflatoxin B_1 exposure
- Metabolic syndrome (NAFLD/NASH)
- Alcohol abuse
- Iron-overload (inherited and acquired)

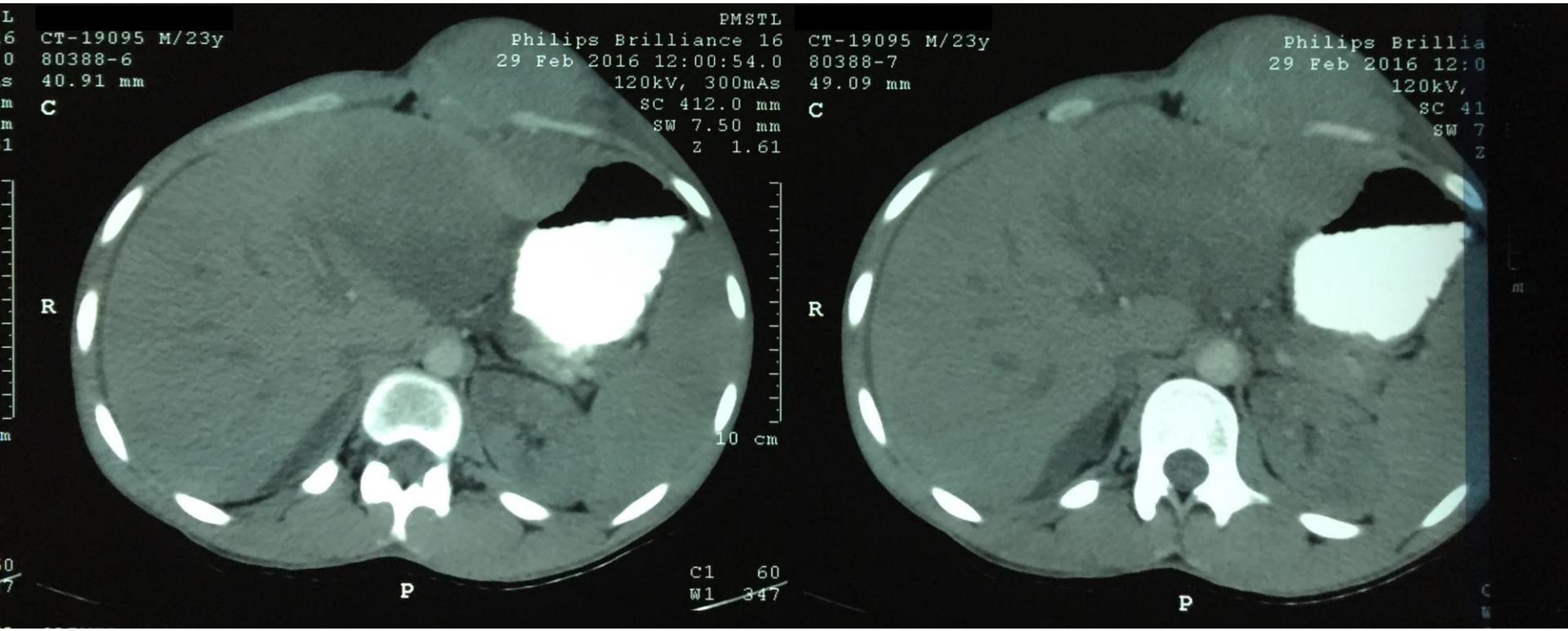
- Cirrhosis of any cause
- Smoking
- Tyrosinosis
- α_1 antitrypsin deficiency
- etc.

Etiology in Africa

- Historic main etiological factors
  - chronic hepatitis B infection
  - aflatoxin exposure
  - dietary iron overload
- Emerging etiological factors
  - alcoholic liver disease
  - NAFLD/NASH
  - chronic hepatitis C

Clinical presentation

- Symptomatic tumour
- Incidental finding examining liver disease
- Screening of high-risk populations


CT-19095 M/23y
80388-6
40.91 mm
C
PMSTL
Philips Brilliance 16
29 Feb 2016 12:00:54.0
120kV, 300mAs
SC 412.0 mm
SW 7.50 mm
Z 1.61
R
10 cm
P
C1 60
W1 347
CT-19095 M/23y
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49.09 mm
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120kV,
SC 41
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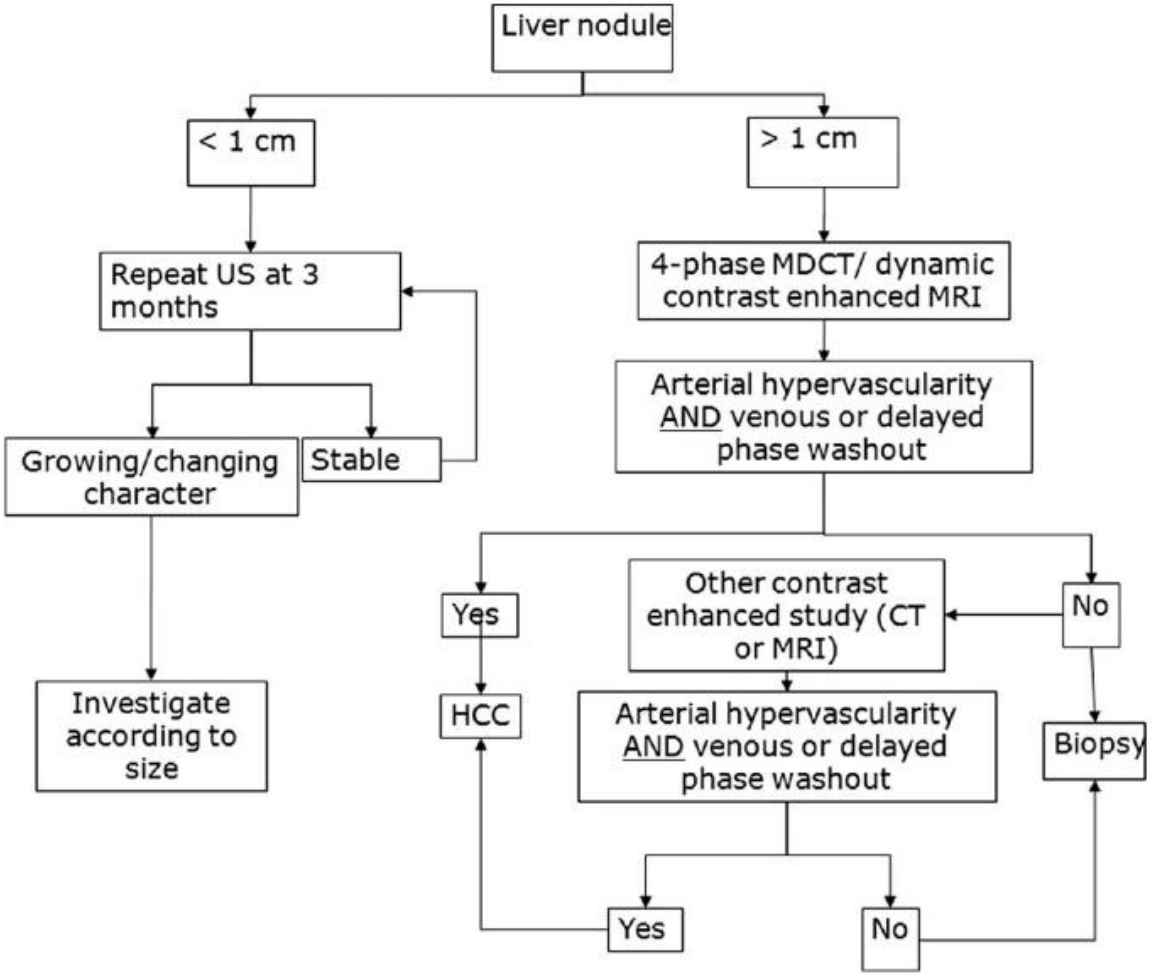
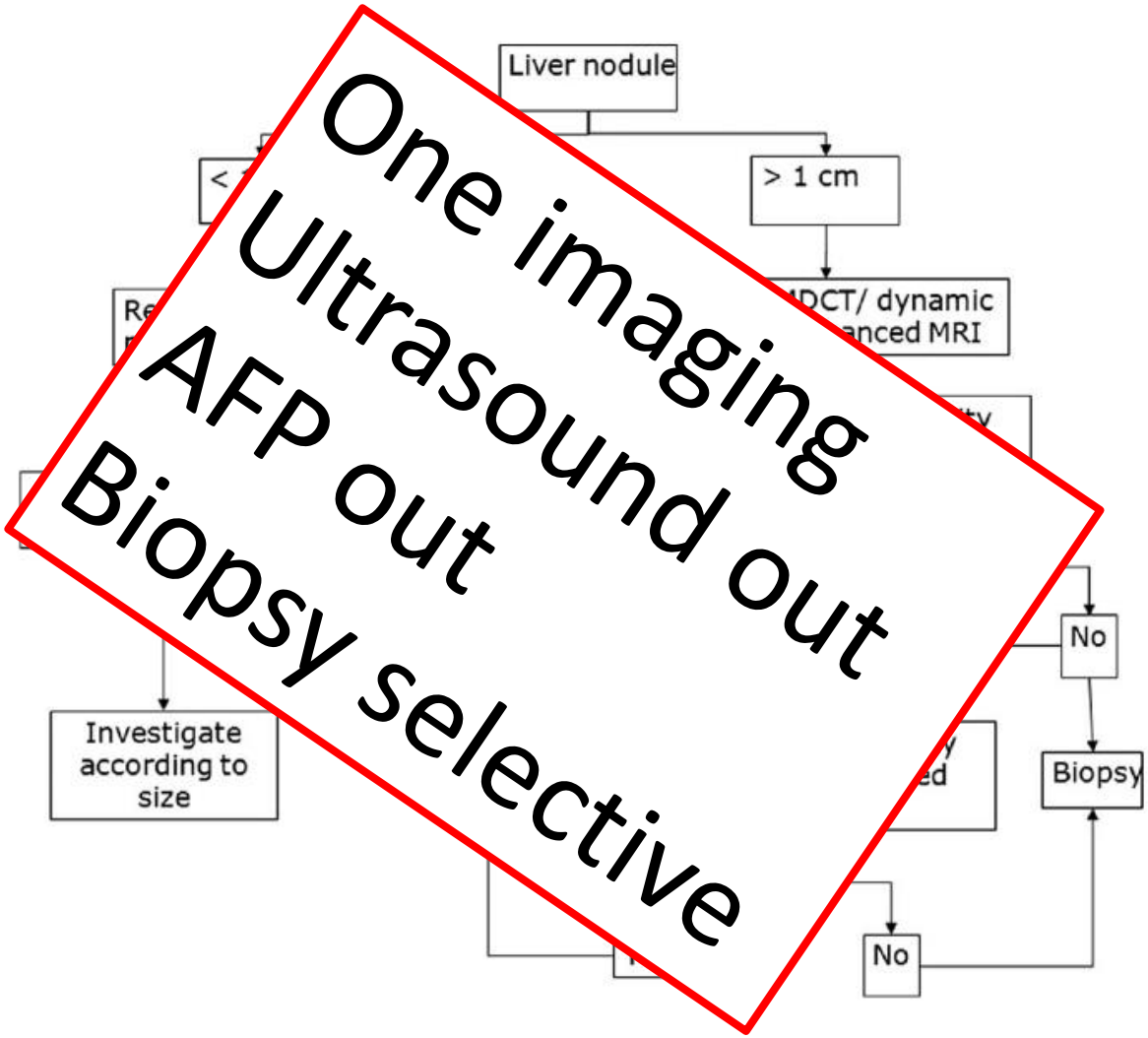
Diagnosis and staging

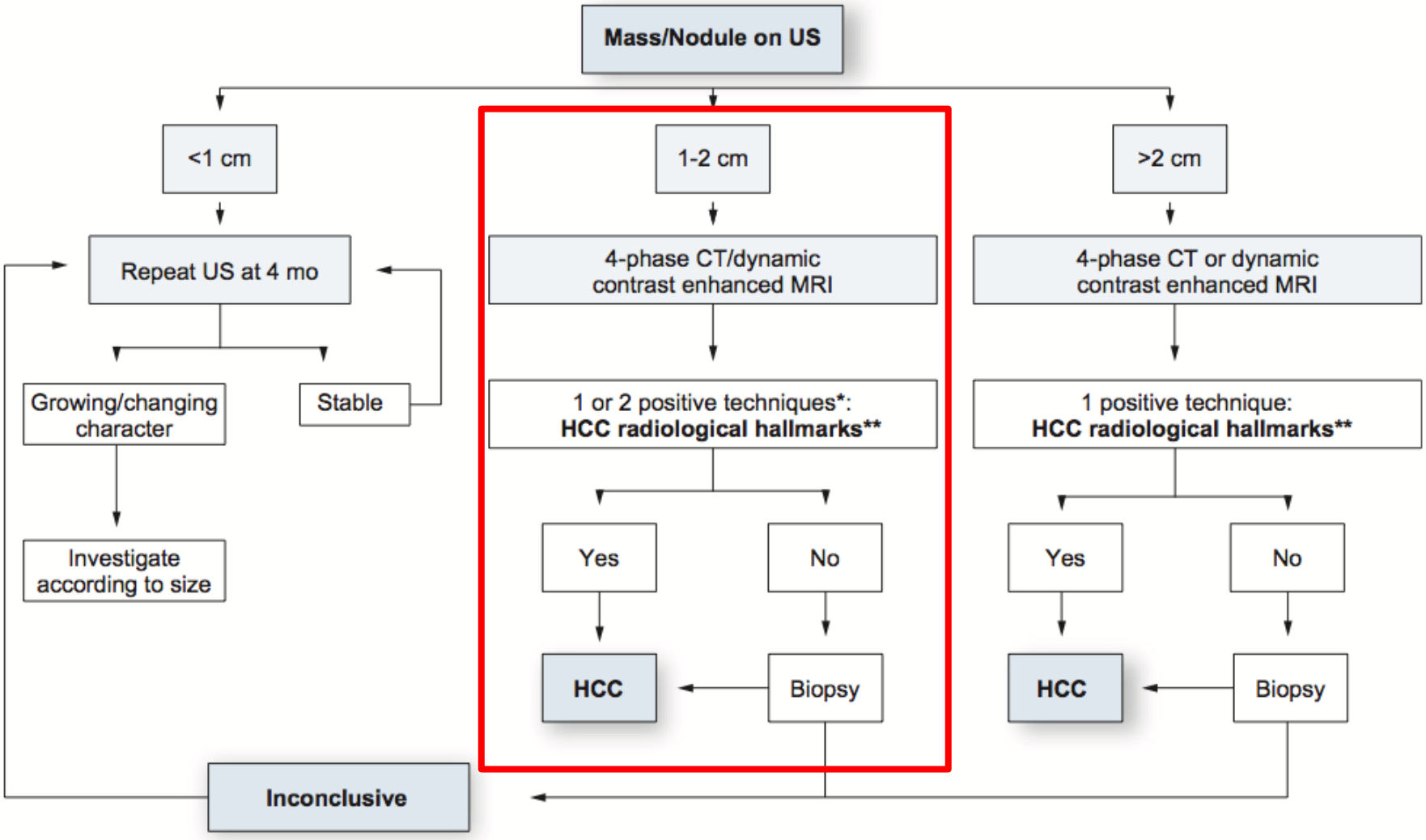


Bruix et al. Hepatology 2011;53:1020-2

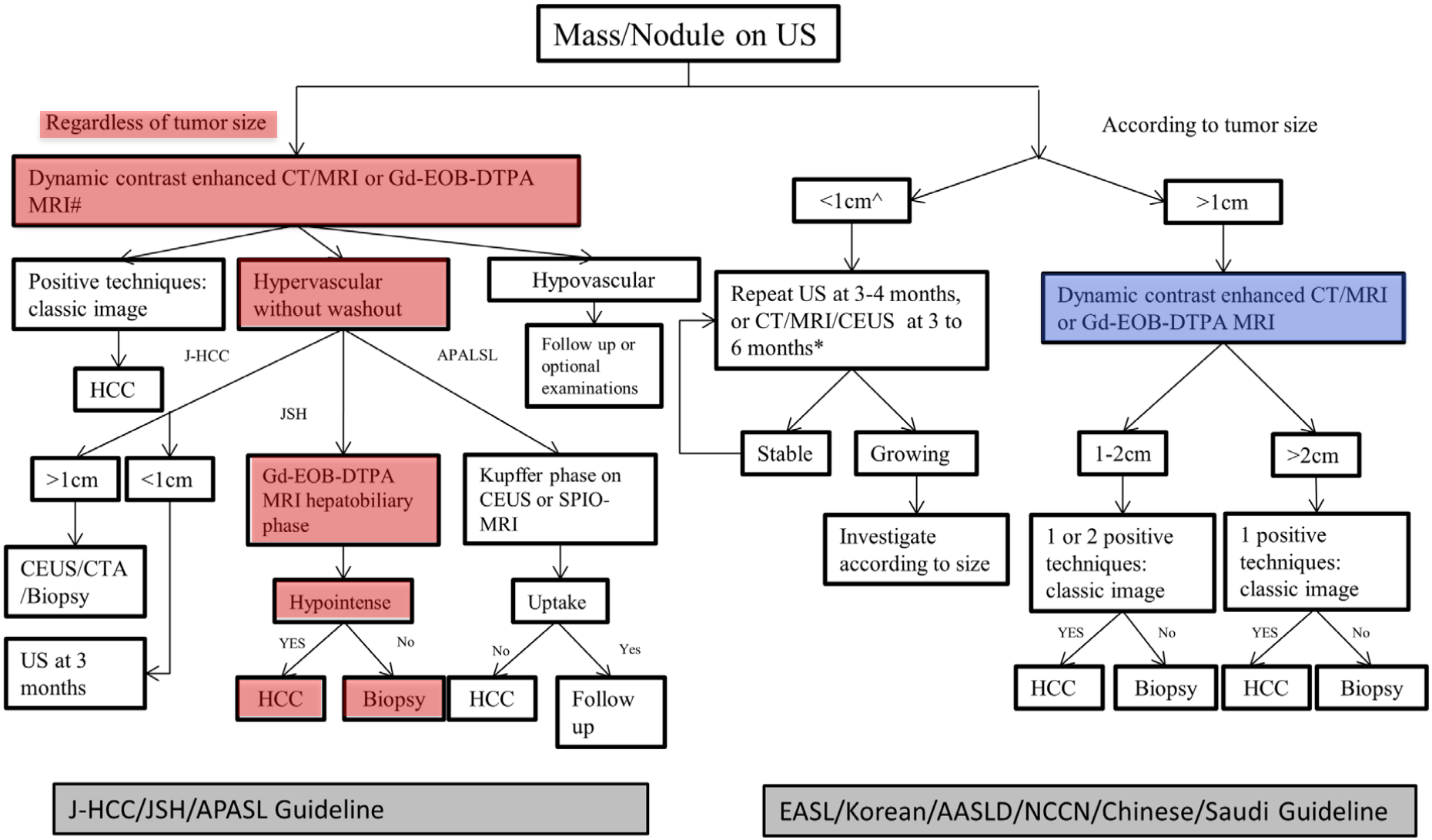
Diagnosis and staging



Bruix et al. Hepatology 2011;53:1020-2



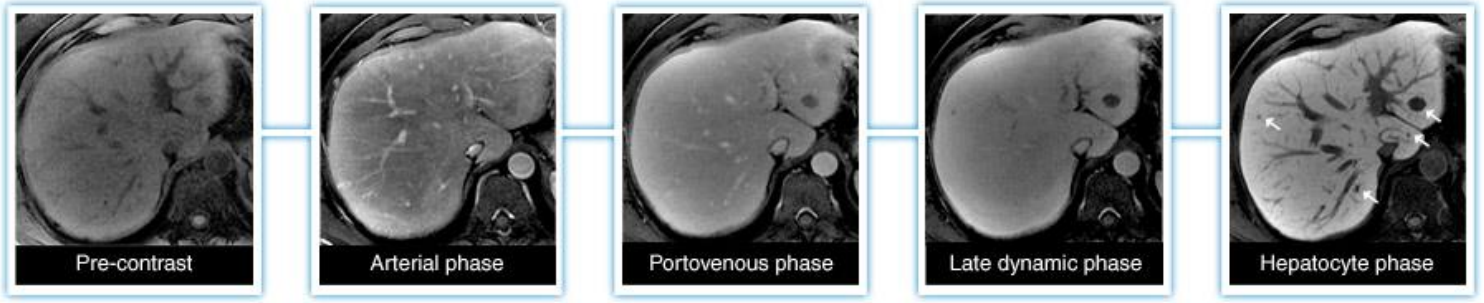
Llovet et al. Journal of Hepatology 2012;56:908-943



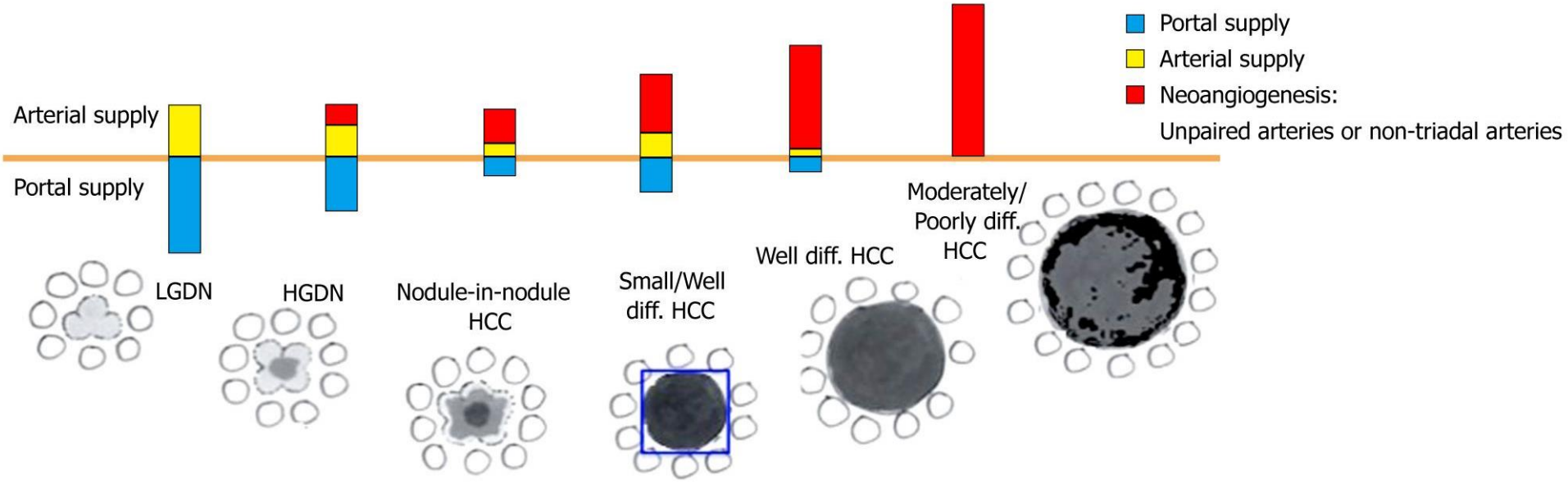
Song P, et al. BioScience Trends. 2017; 11:389-398

Gd-EOB-DTPA (Primovist® /Eovist®)
Gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid

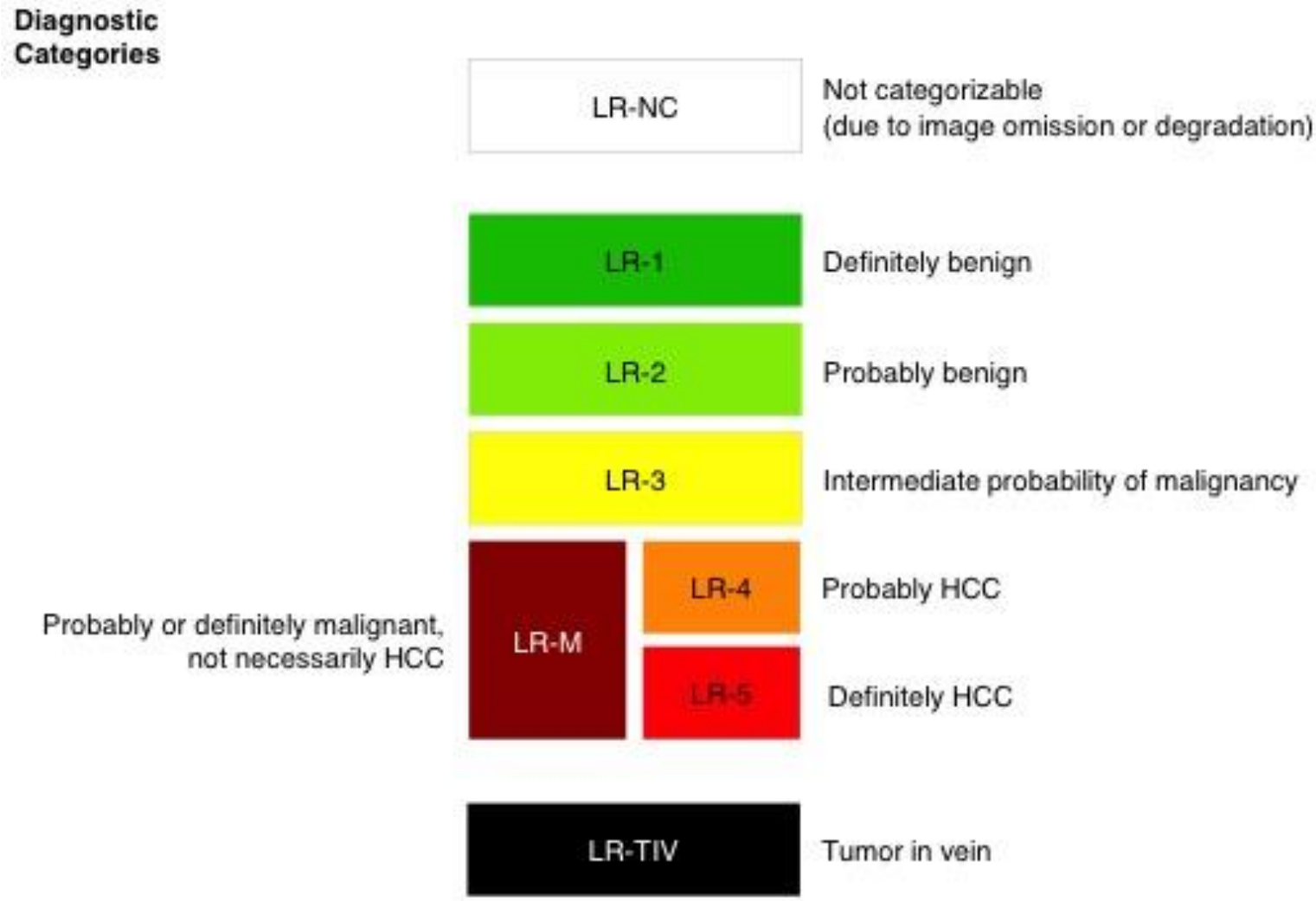
	Pre-contrast	Arterial phase	Portovenous phase	Delayed phase	Hepatobiliary phase
CE-MDCT	✓	✓	✓	✓	X
ECCM-MRI	✓	✓	✓	✓	X
Gd-EOB-DTPA-MRI	✓	✓	✓	✓	✓



CE-MDCT	contrast-enhanced multi-detector computed tomography
ECCM-MRI	MRI with extracellular contrast media
Gd-EOB-DTPA-MRI	gadoxetic acid-enhanced MRI


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

The Liver Imaging Reporting And Data System (LI-RADS)

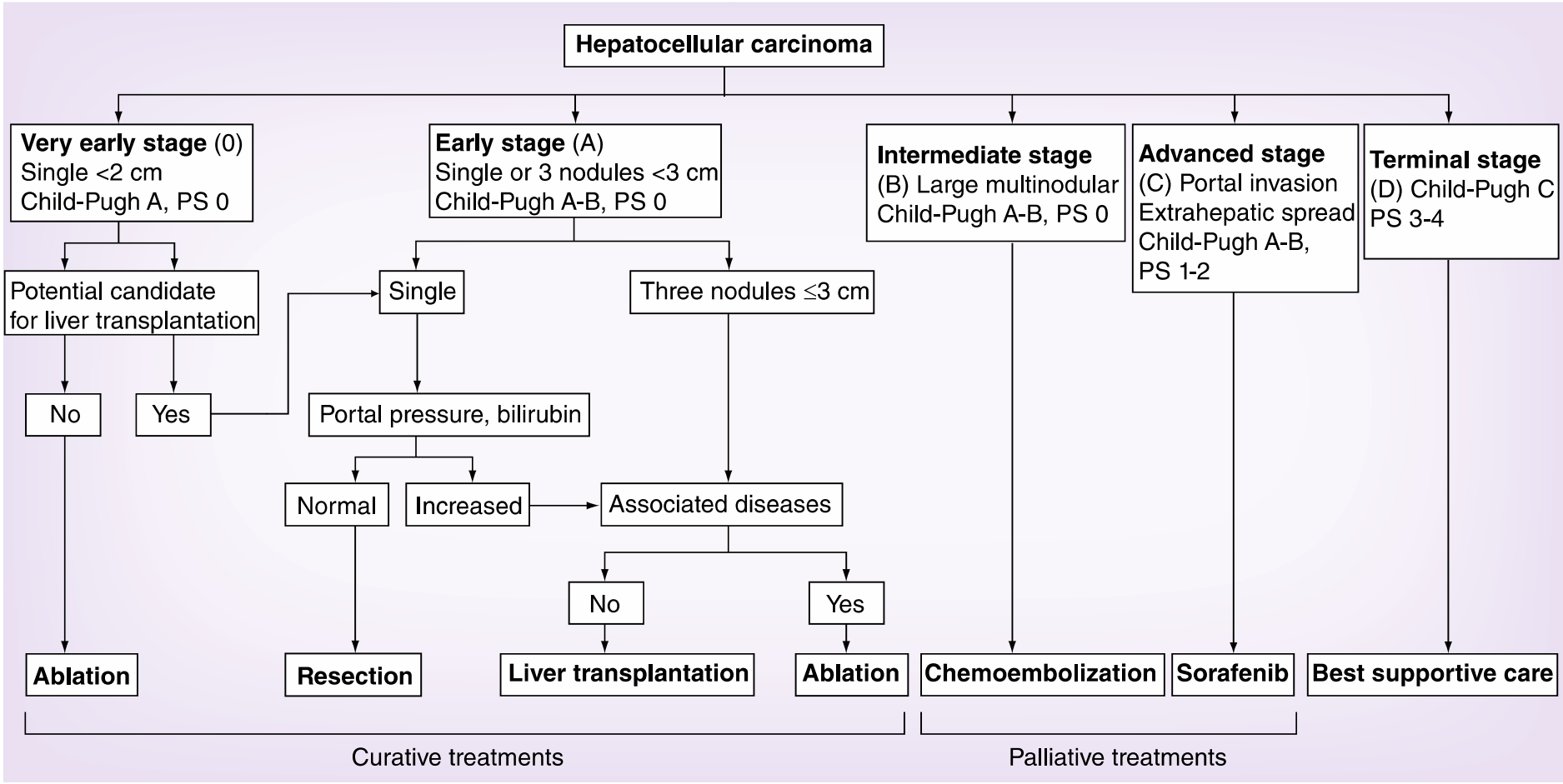


Treatment Response Categories

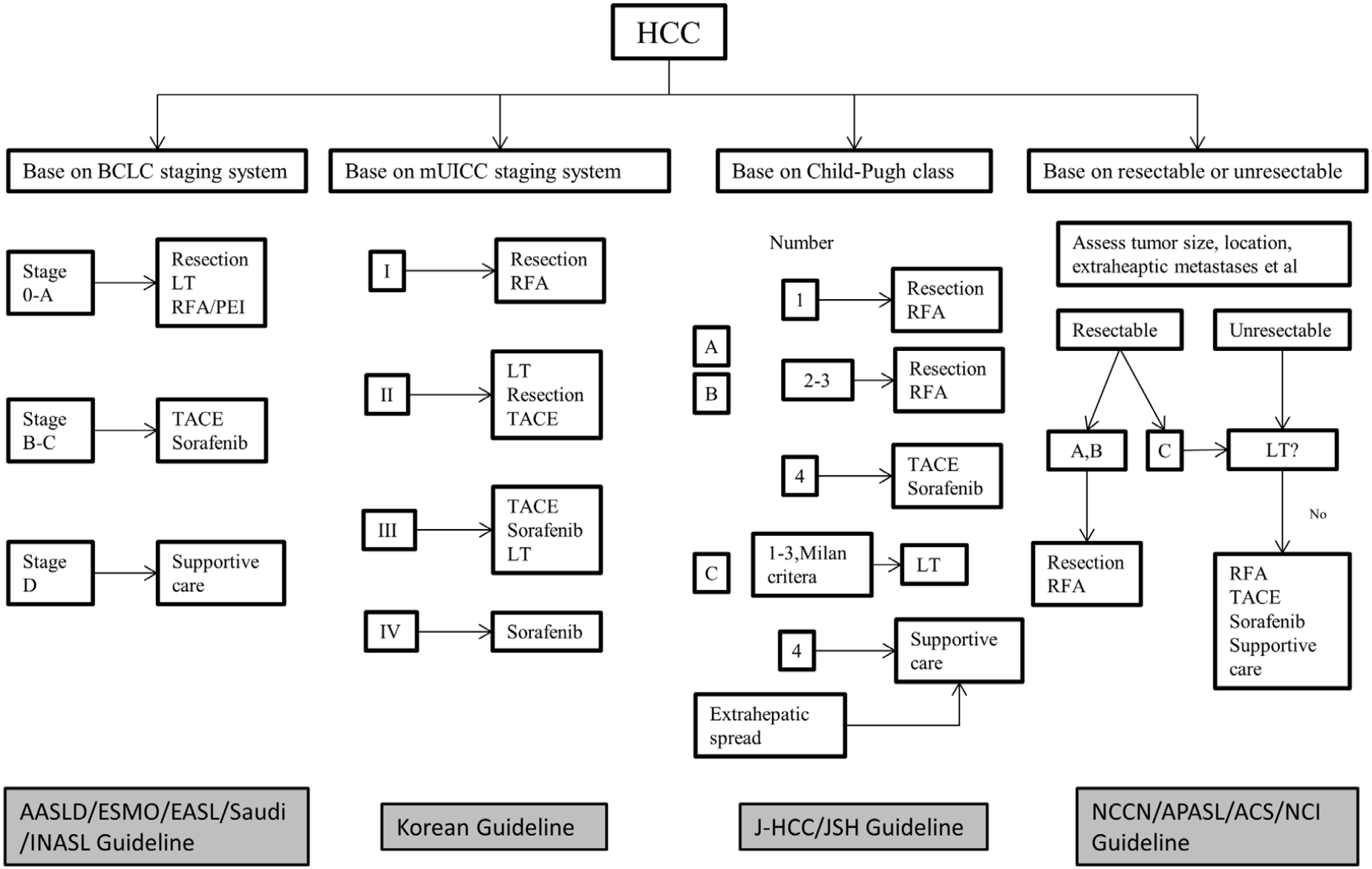
Treatment

- Based on the Barcelona Clinic Liver Cancer (BCLC) staging system
- Based on the modified Union of International Cancer Control (mUICC) staging system
- Based on the Child-Pugh class of liver function
- Based on tumor resectability (resectable or unresectable)

Treatment



Forner A, et al. Hepatocellular carcinoma. Lancet 2012;379:1245–1255



Song P, et al. BioScience Trends. 2017; 11:389-398

The unmet clinical needs of the BCLC guidelines

- Assumptions
  - Universally homogenous disease
  - Homogenous stage stratification
  - Work-up possibilities are available
  - All treatment possibilities are available

- Does not account for heterogeneity
  - Exists for stage A
  - Lacking stage B

Heterogeneity of Patients with Intermediate (BCLC B) Hepatocellular Carcinoma: Proposal for a Subclassification to Facilitate Treatment Decisions

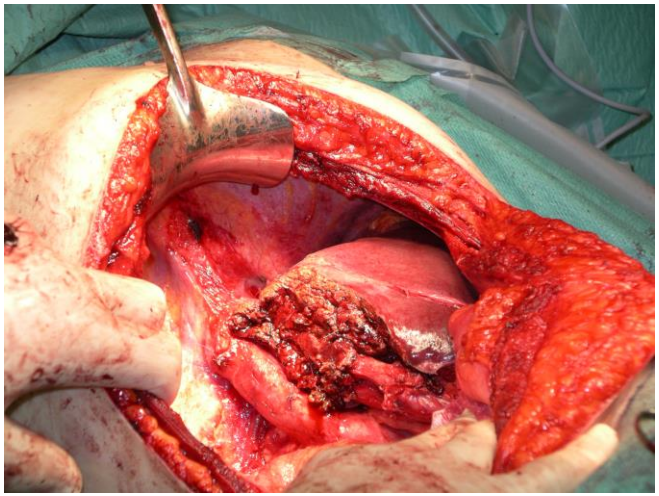
Luigi Bolondi, MD[1] Andrew Burroughs, MBChBHons, FMedSci[1] Jean-François Dufour, MD[1]
Peter R. Galle, MD, PhD[1] Vincenzo Mazzaferro, MD[1] Fabio Piscaglia, MD, PhD[1]
Jean Luc Raoul, MD, PhD[1] Bruno Sangro, MD, PhD[1Q1]

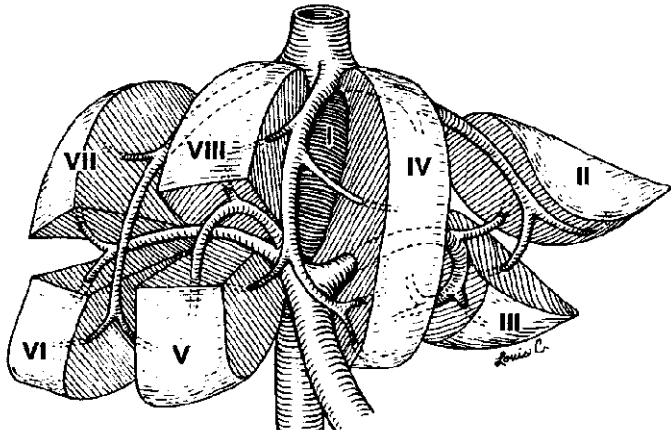
	Examples of Patients with Intermediate HCC			
	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**
Bilirubin (mg/dl)	0.9	1.6	2.6	1.9
Albumin (g/dl)	4.8	3.6	3.0	2.7
Ascites	No	Mild	Mild	Refractory
Hepatic encephalopathy	No	No	No	No
Child–Pugh class	A	A	B	B
Number of HCC tumors	2	4	1	4
Diameter of the 2 largest HCC	35–16 mm	60–45 mm	19–18 mm	19–18 mm
Potential treatment	Surgery versus combined TACE + ablation	TACE	TACE (?)	None
Potential for cure (estimated probability of total tumor necrosis)[†]	65%	20%	<5%	0%

Bolondi L, et al. Semin Liver Dis 2012;32:348–359

Liver resection
Principles

- R0 resection
- Sufficient future liver remnant
- No extra-hepatic metastases





Liver resection
Current guidelines

Barcelona criteria

Very early stage (0)

- Single lesions
- < 2 cm in size

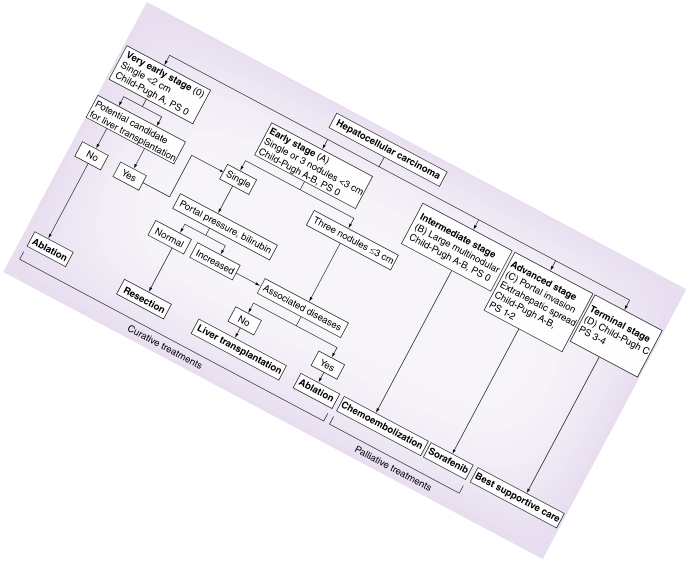
} tumour

- Child-Pugh score A
- Normal portal pressure
- Normal bilirubin

} function surrogates

- Performance status 0

} general condition



Liver resection
Current clinical practice

Guidelines are challenged:

- Multiple lesions
- Large lesions
- Portal hypertension

Liver resection
Results

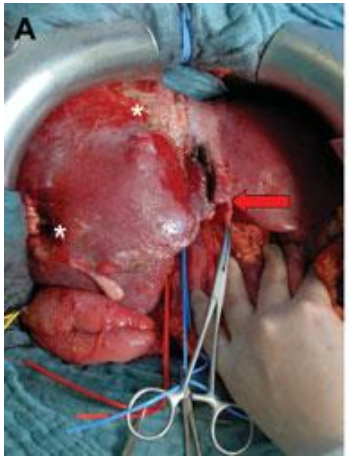
Table 1 Results of liver resection in a recently published surgical series (after 2005) in which surgery was performed beyond the beyond barcelona clinic liver cancer recommendations

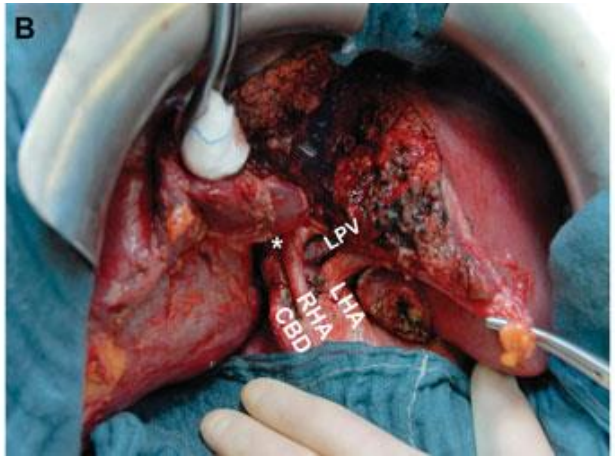
Ref.	Year	Patients (*n*)	Mortality/morbidity	5-yr survival
BCLC 0-A HCC with portal hypertension				
Capussotti *et al*[43]	2006	66	6.1%/34.8%	40.80%
Ishizawa *et al*[51]	2008	136	-/10%	56.00%
Cucchetti *et al*[44]	2009	79	4.5%/38.5%	56.50%
Ruzzenente *et al*[46]	2011	29	2.2%/33.7%	57.3%(72.4%)[1]
Santambrogio *et al*[45]	2013	63	0.5%/28.6%	48.00%
BCLC A-B multiple HCCs				
Ishizawa *et al*[51]	2008	126	-/15%	58.00%
Ruzzenente *et al*[33]	2009	30 (≤ 3 nodules)	-/-	46.00%
Ho *et al*[59]	2009	97 (≤ 3 nodules)	-/-	40.00%
Huang *et al*[57]	2010	26 (≤ 3 nodules)	0%/27.8%	69.20%
Torzilli *et al*[25]	2013	54 (> 3 nodules)	-/-	12.00%
Zhong *et al*[29]	2013	58 (> 3 nodules)	3.1%[2]/28.0%[2]	24.00%
BCLC B large HCC				
Pawlik *et al*[64]	2005	300 (≥ 10 cm)	5.0%/-	27.00%
Pandey *et al*[62]	2007	166 (≥ 10 cm)	3.0%/30.0%	28.60%
Cho *et al*[63]	2007	61 (> 5 cm)	1.6%/-	52.90%
Ruzzenente *et al*[33]	2009	46 (> 5 cm)	-/-	29.00%
Yamashita *et al*[65]	2011	53 (≥ 10 cm)	3.8%/24.5%	35.00%
Zhong *et al*[29]	2013	199 (> 5 cm)	3.1%[2]/28.0%[2]	41.00%
BCLC C HCC with macrovascular invasion				
Pawlik *et al*[32]	2005	102 (PVTT and HVI)	5.9%/-	10.00%
Le Treut *et al*[84]	2006	26 (PVTT and HVI)	11.5%/38.5%	13.00%
Ruzzenente *et al*[33]	2009	17 (PVTT and HVI)	-/-	20.00%
Inoue *et al*[81]	2009	49 (PVTT)	0%/-	39%-41%
Ban *et al*[82]	2009	45 (PVTT)	0.0%/21.1%-23.1%	22.40%
Chok *et al*[79]	2013	88 (PVTT)	3.4%/37.1%	11.2%-14.3%
Wang *et al*[76]	2013	25 (HVI)	0.0%/40.0%	13.50%

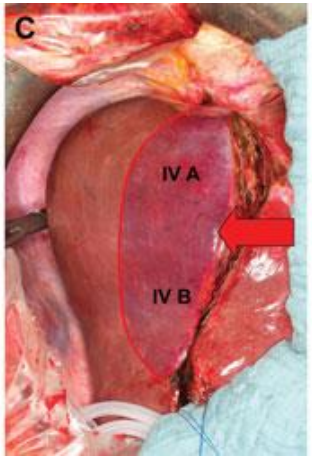
Guglielmi A, et al. World J Gastroenterol.2014;20:7525-7533

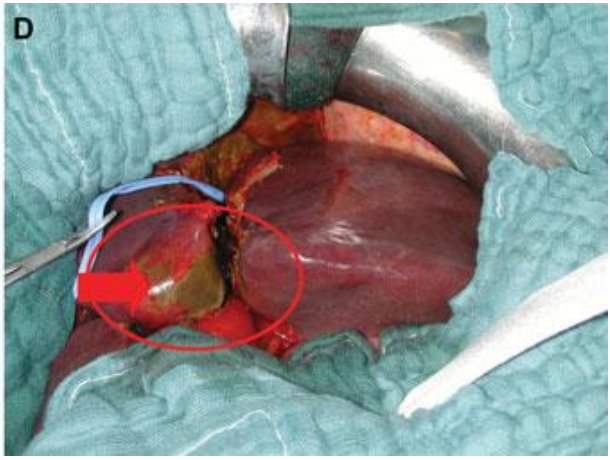
Right Portal Vein Ligation Combined With In Situ Splitting Induces Rapid Left Lateral Liver Lobe Hypertrophy Enabling 2-Staged Extended Right Hepatic Resection in Small-for-Size Settings

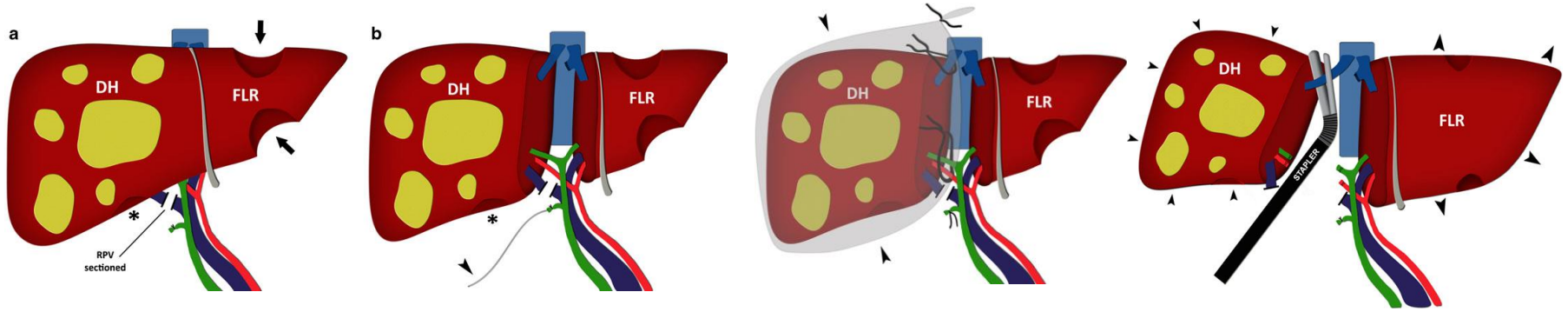
Andreas A. Schnitzbauer, MD, Sven A. Lang, MD,* Holger Goessmann, MD,† Silvio Nadalin, MD,§ Janine Baumgart, MD,|| Stefan A. Farkas, MD,* Stefan Fichtner-Feigl, MD,* Thomas Lorf, MD,¶ Armin Goralcyk, MD,¶ Rüdiger Hörbelt, MD,# Alexander Kroemer, MD,* Martin Loss, MD,* Petra Rümmele, MD,‡ Marcus N. Scherer, MD,* Winfried Padberg, MD,# Alfred Königsrainer, MD,§ Hauke Lang, MD,|| Aiman Obed, MD,¶ and Hans J. Schlitt, MD**





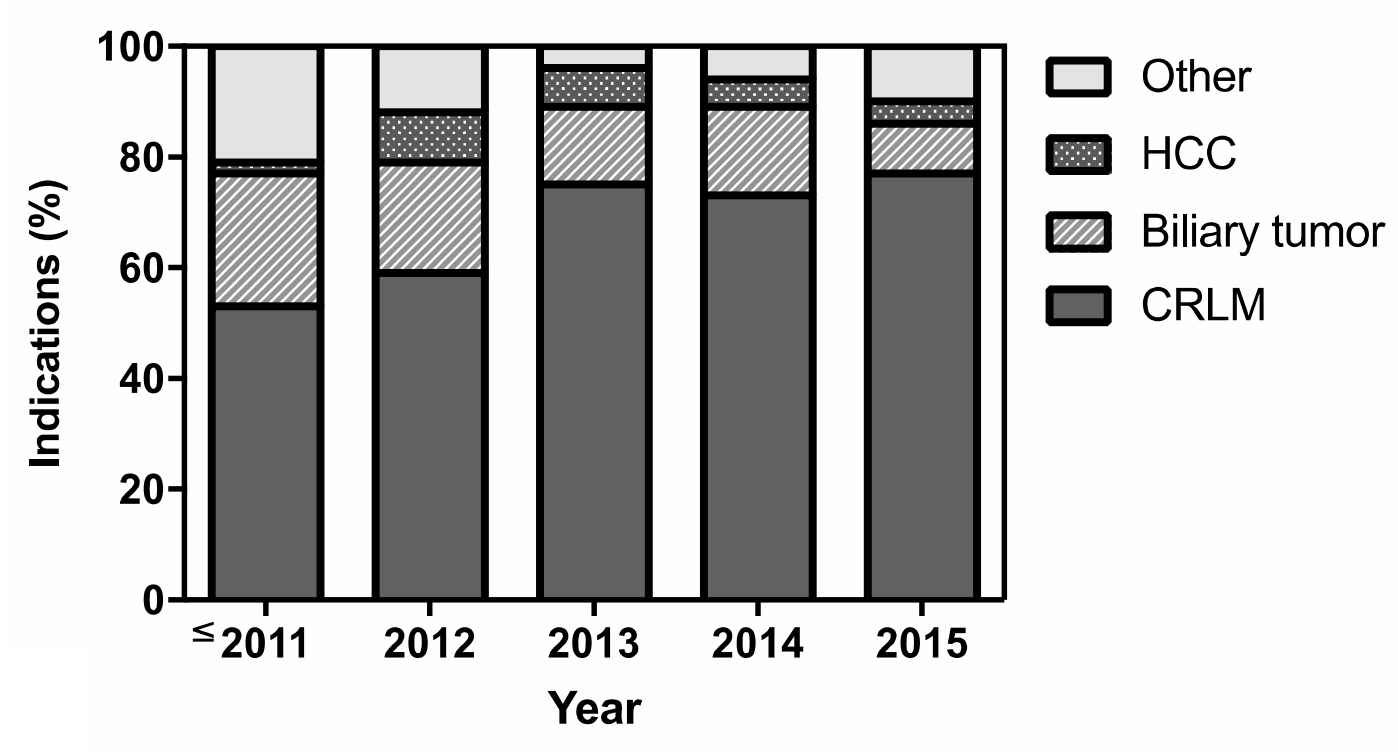






Schnitzbauer AA, et al. Ann Surg. 2012;255:405-14

Current indications



Linecker M, et al. Surgery 2017;161:453-464

Liver transplantation
Principles

- Removes tumour
- Cures liver dysfunction
- Prevents new tumour formation, **not** metastases
- Patients with low risk for metastatic disease are selected

- HCC transplants compete with other indications
- Highly dependent on donor supply

Liver transplantation

Current guidelines

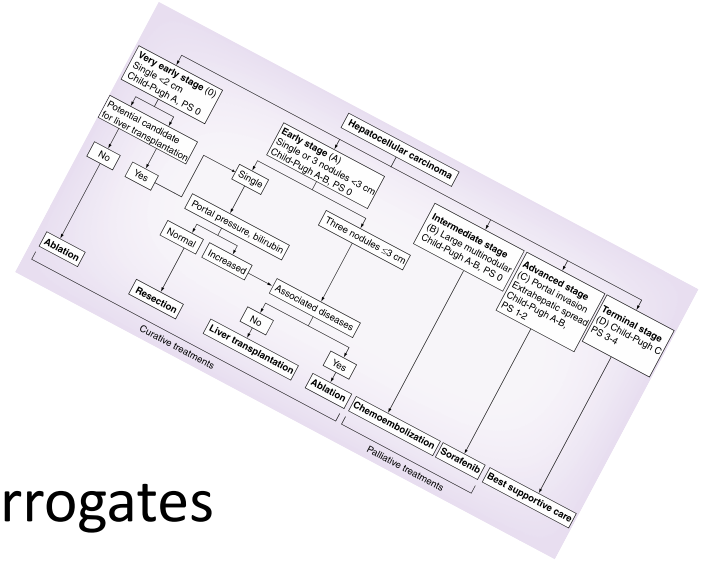
Barcelona criteria

Very early or early stage (0;A)

- 1-3 lesions*
- ≤3 cm in diameter*

} tumour

- Child-Pugh score A-B } function surrogates
- Performance status 0 } general condition



* Milan criteria – ≤5 cm was added as a size limitation for single lesions

OS when transplanted within the BCLC >70% at 5 years

Liver transplantation

Current clinical practice

Expanding transplant criteria

Cons

- Increase need for organs
- Increase waiting times
- Saturating waiting lists with worse outcomes
- Increase drop-outs
- Impairs intention-to-treat results

Milan criteria

- 1 lesion ≤5 cm
- 3 lesions ≤3 cm in diameter

University of California San Francisco (UCSF) criteria

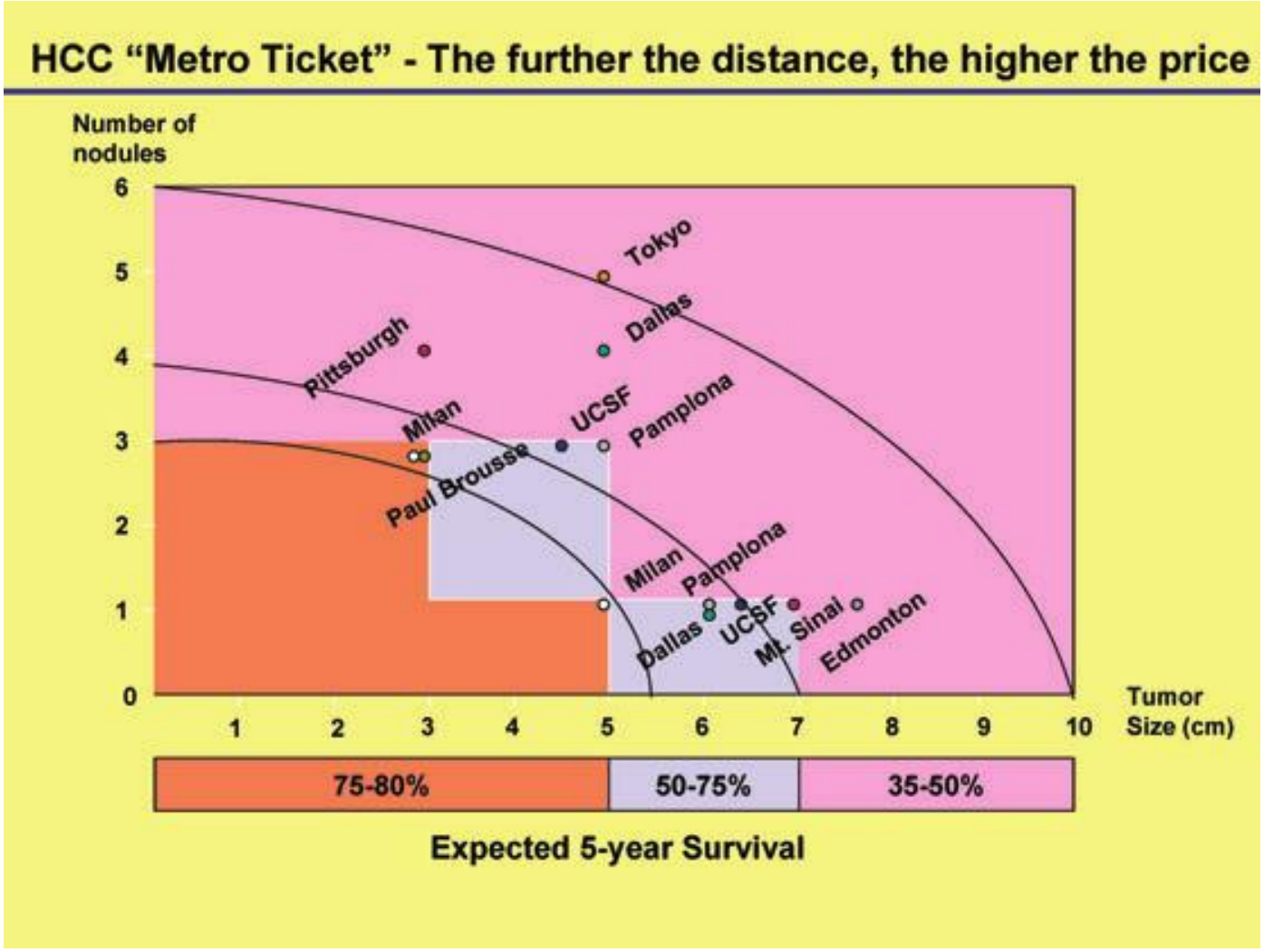
- 1 nodule ≤ 6.5 cm
- or 2–3 nodules ≤ 4.5 cm; total tumour diameter ≤ 8 cm

‘Up-to-seven’ criteria

- sum of the size of largest tumour and tumour number ≤ 7

Yao FY, et al. Hepatology 2001;33:1394–403
Mazzaferro V, et al. N Engl J Med 1996; 334: 693–9

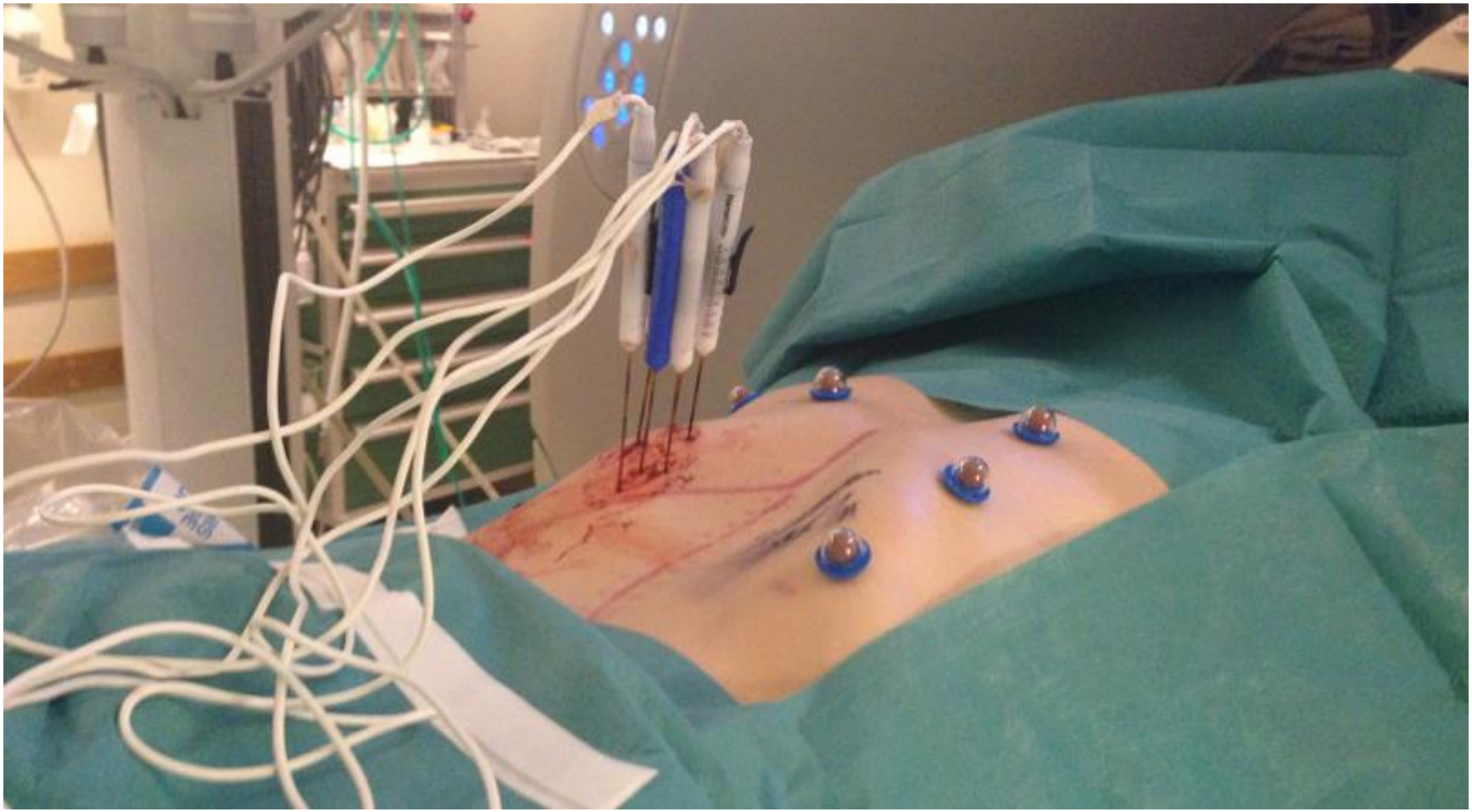
HCC Metro ticket



Local ablation
Principles

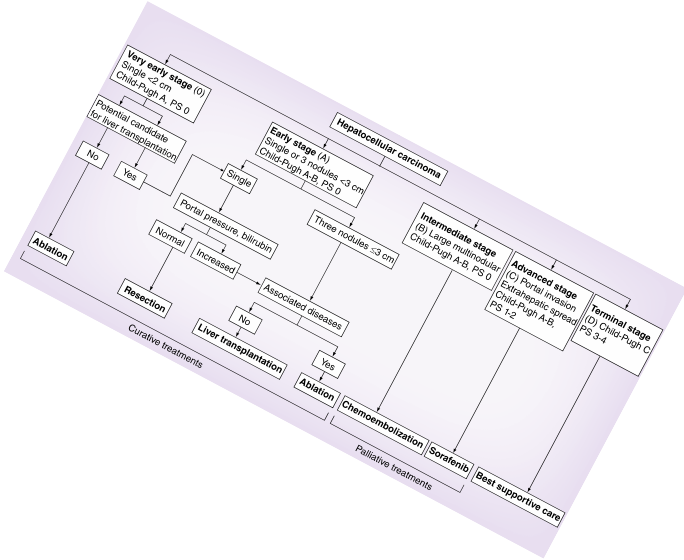
- Radiofrequency ablation (RFA) ✓
- Microwave ablation (MWA) ✓
- Laser ablation (LA) ✗
- Cryoablation ✗
- Ethanol ablation ✓✗
- Irreversible electroporation (IRE) ✓
- High-intensity focused ultrasound (HIFU) ✗
- Stereotactic body radiation therapy (SBRT) ✓✗

Completed Needle Placement



Local ablation

Current guidelines



Barcelona criteria

Very early or early stage (0;A)

- 1-3 lesions
- ≤3 cm in diameter

} tumour

- Child-Pugh score A/B

} function surrogates

- Performance status 0

} general condition

Local ablation

Current practice

> 3 cm in size – increase in local recurrence rates

> 3 lesions – oncological more advanced

Local ablation
Results

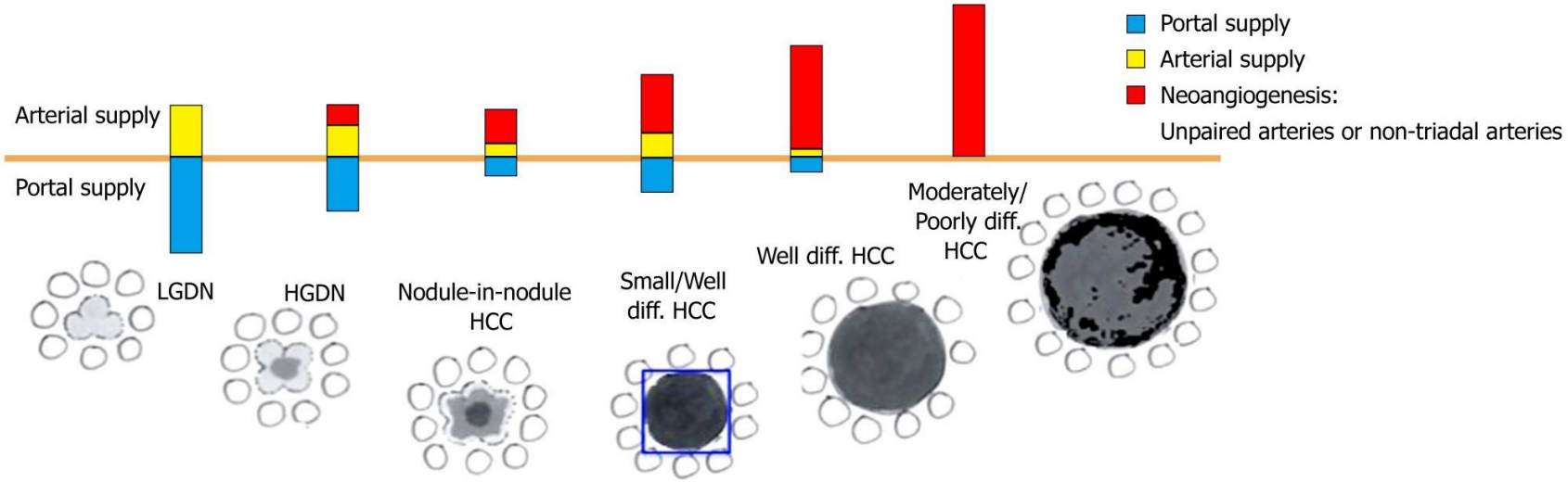
Median overall survival

	Within	**Outside**
1 year	96–100 %	78 – 98 %
3 year	53–92 %	33–94 %
5 year	41–77 %	20–75 %

Tiong L, et al. British Journal of Surgery 2011;98:1210–1224

Embolization

Principles



Embolization
Principles

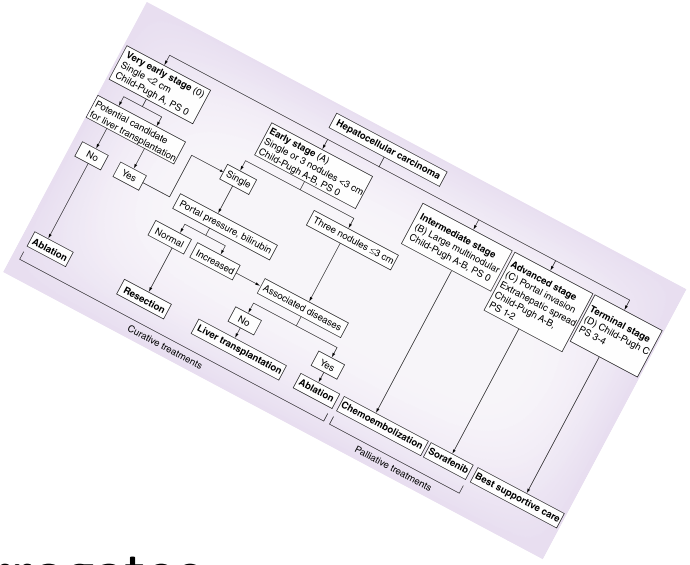
- Transarterial embolization (TAE)

- Transarterial chemoembolization (TACE)
  - conventional – Doxorubicin/Lipiodol emulsion
  - Doxorubicin-loaded drug-eluting beads (DEB)

- Transarterial radioembolization (TARE)
  - Iodine-131-labelled Lipiodol
  - microspheres loaded with Yttrium-90 (β emitter with short tissue penetration)

Llovet JM, Bruix J. Hepatology 2003;37:429–42

Embolization
Current guidelines



Barcelona criteria

Intermediate stage (B)

- Large multi-nodular — tumour
- Child-Pugh score A/B — function surrogates
- Performance status 0 — general condition

Llovet JM, Bruix J. Hepatology 2003;37:429–42

Embolization
Current practice

Embolization outside the BCLC criteria

Indication

- Intermediate-stage (BCLC B) HCC

Absolute contraindications

- Child-Pugh B ≥8
- Extensive tumour with massive replacement of both entire lobes
- Severely reduced portal vein flow (portal vein occlusions; hepatofugal blood flow)
- Untreatable arteriovenous fistula
- Renal failure (creatinine ≥2 mg/dL; creatinine clearance <30 mL/ min)

Relative contraindications

- Tumour size ≥10 cm
- Compromised organ function (active cardiovascular disease; active lung disease)
- Untreated varices at high risk of bleeding
- Bile-duct occlusion or incompetent papilla due to stent or surgery

Raoul JL, et al. Cancer Treat Rev 2011;37:212–20

Embolization
Results

- Heterogeneity in reported overall survival
- **Prospective studies:** mean OS 3.4-31 months
- **Retrospective studies:** mean OS 8.5-48 months
- Doxorubicin-loaded drug-eluting beads (DEB) can cause complete necrosis of <5 cm HCC nodules
- TARE - ? curative modality

Oncologic treatment

Sorafenib (Nexavar)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sorafenib in Advanced Hepatocellular Carcinoma

- Median OS - 10.7 months in the sorafenib group vs. 7.9 months in the placebo group ($p<0.001$)
- Modest advantage

Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial

- Median recurrence-free survival – 33.3 months in the sorafenib group vs 33.7 months in the placebo group ($p=0.26$)
- No advantage

Llovet JM, et al. N Engl J Med. 2008;359:378-90
Bruix J, eta..Lancet Oncol 2015; 16: 1344–54

Table 1
Hepatocellular carcinoma subtypes

Subtype	Frequency in Surgical Pathology Specimens (%)	Prognosis[a]
Steatohepatitic	20	Similar
Clear cell	7	Better
Scirrhous	4	Similar to better
Cirrhotomimetic	1	Worse
Combined hepatocellular-cholangiocarcinoma	1	Worse
Fibrolamellar carcinoma	1	Similar to better
Combined hepatocellular and neuroendocrine	<1	Worse
Granulocyte colony-stimulating factor producing	<1	Worse
Sarcomatoid	<1	Worse
Carcinosarcoma	<1	Worse
Carcinosarcoma with osteoclast-like giant cells	<1	Worse
Lymphocyte rich	<1	Better
Provisional subtypes		
Chromophobe	1–2	Unclear
Combined hepatocellular-cholangiocarcinoma with stem cell features	<1	Unclear
Lipid rich	<1	Unclear
Myxoid	<1	Unclear
Syncytial giant cell	<1	Unclear
Transitional cell	<1	Unclear

[a] Compared with conventional hepatocellular carcinoma.

Review Article

Systemic therapy for advanced hepatocellular carcinoma: an update

Jasmin Radhika Desai[1], Sebastian Ochoa[2], Petra Alexandra Prins[1], Aiwu Ruth He[1]

Table 1 Relative frequency of genetic mutations in HCC

Pathway and function	Target	Prevalence (%)
Telomere stability	TERT promoter	60
Wnt/ß-catenin pathway	CTNNB1	40
p53/cell cycle control	TP53	25
Chromatin remodeling	ARID1A	15
RAS/PI3K /mTOR	RPS6KA3	10
FGF signaling	FGF19	5
VEGF signaling	VEGFA	3

HCC, hepatocellular carcinoma.

Table 2 Selected drugs for HCC treatment and their molecular targets

Drug	Target
ADI-PEG20	Arginine
Bevacizumab	VEGF
Brivanib	VEGFR-2, FGFR-1
Cabozantinib	VEGFR, RET, c-MET
Cediranib	VEGFR, PDGFR, c-KIT
Cixutumumab	IGF-1R
Erlotinib	EGFR
Everolimus	mTOR
Ipilimumab	CTLA-4
Lenvatinib	VEGFR, PDGR, FGFR, RET, SCFR
Linifanib	VEGFR, PDGFR
Nivolumab	PD-1
Orantinib	VEGFR, PDGFR, FGFR
Ramucirumab	VEGFR
Regorafenib	VEGFR, PDGFR, RET, c-KIT, BRAF, FGFR
Sorafenib	VEGFR, PDGFR, RAF
Sunitinib	VEGFR, PDGFR, RET, c-KIT
Tivantinib	c-MET
Tremelimumab	CTLA-4

HCC, hepatocellular carcinoma.

Desai J, et al. J Gastrointest Oncol 2017;8:243-255

Prognosis

- Liver resection* >70% 5 year survival
- Local ablation* >70% 5 year survival
- Transplantation* >75% 5 year survival
- TACE 20 mo improved survival
- Sorafenib 2.9 mo improved survival
- Best supportive care

*Treated within the Barcelona criteria

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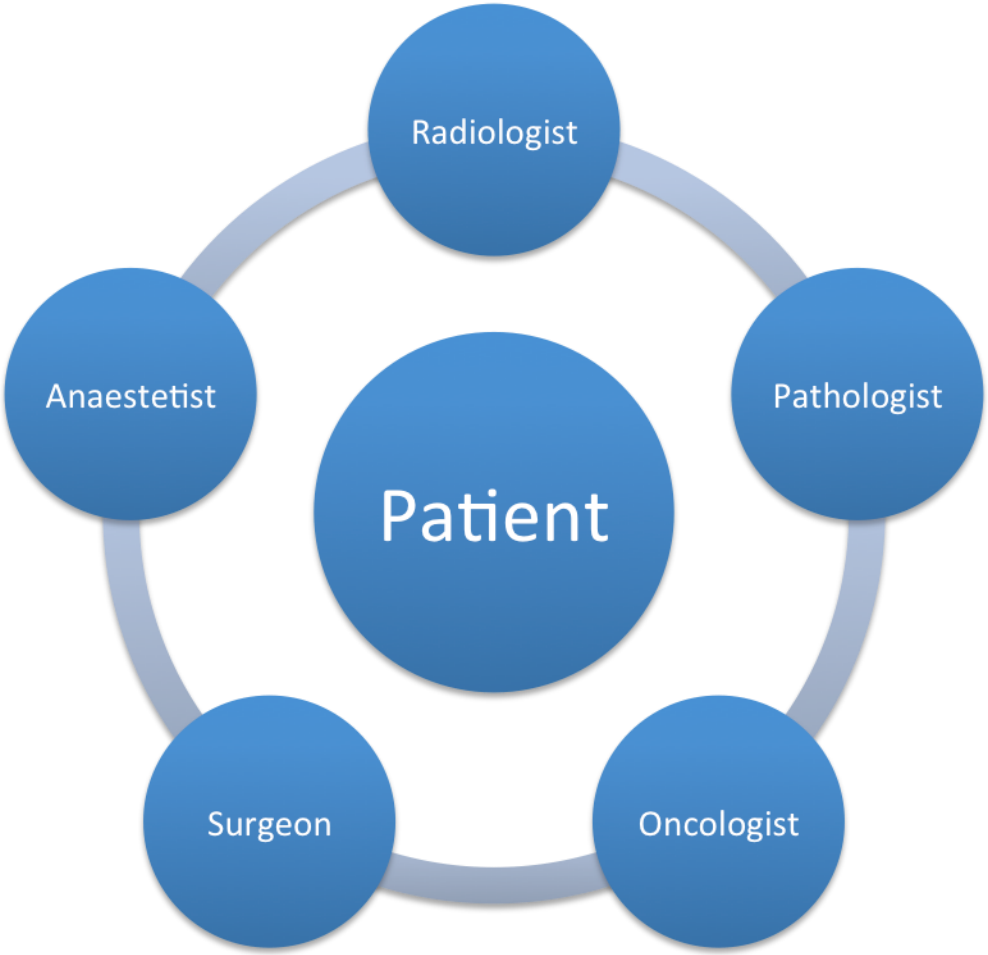
MDT conference



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Thank you

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