Surgical resection for hepatocellular carcinoma (HCC)

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1st Maastricht E-AHPBA Post-Graduate HPB Course

Maastricht June 2-3, 2016

I have nothing to disclose

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Introduction

- HCC is the **sixth** most common neoplasm and the **third** leading cause of cancer-related death in the world
- The highest prevalence of this tumor is **in Asia and Africa**, although during the last decades the prevalence in Western countries **in Europe and USA is rising**
- HCC results in between **250,000 and one million deaths** globally per annum
- **Almost 80% cases are due to underlying liver cirrhosis** (chronic HBV or HCV infection)
- Compensated cirrhosis have a **3-4% annual incidence of HCC**, and those with chronic hepatitis have an approximate annual risk of 1%
- HCC is typically diagnosed late and the **median survival following diagnosis is approximately 6-20 months**

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Risk factors for HCC

Geographic area	AAIR	Risk factors		Alcohol	Others
	M/F	HCV (%)	HBV (%)	(%)	(%)
Europe	6.7/2.3	60-70	10-15	20	10
Southern	10.5/3.3				
Northern	4.1/1.8				
North America	6.8/2.3	50-60	20	20	10 (NASH)
Asia and Africa		20	70	10	10 (Aflatoxin)
Asia	21.6/8.2				
China	23/9.6				
Japan	20.5/7.8	70	10-20	10	10
Africa	1.6/5.3				
WORLD	16/6	31	54	15	

EASL-EORTC Clinical Guidelines, J Hepatology 2012

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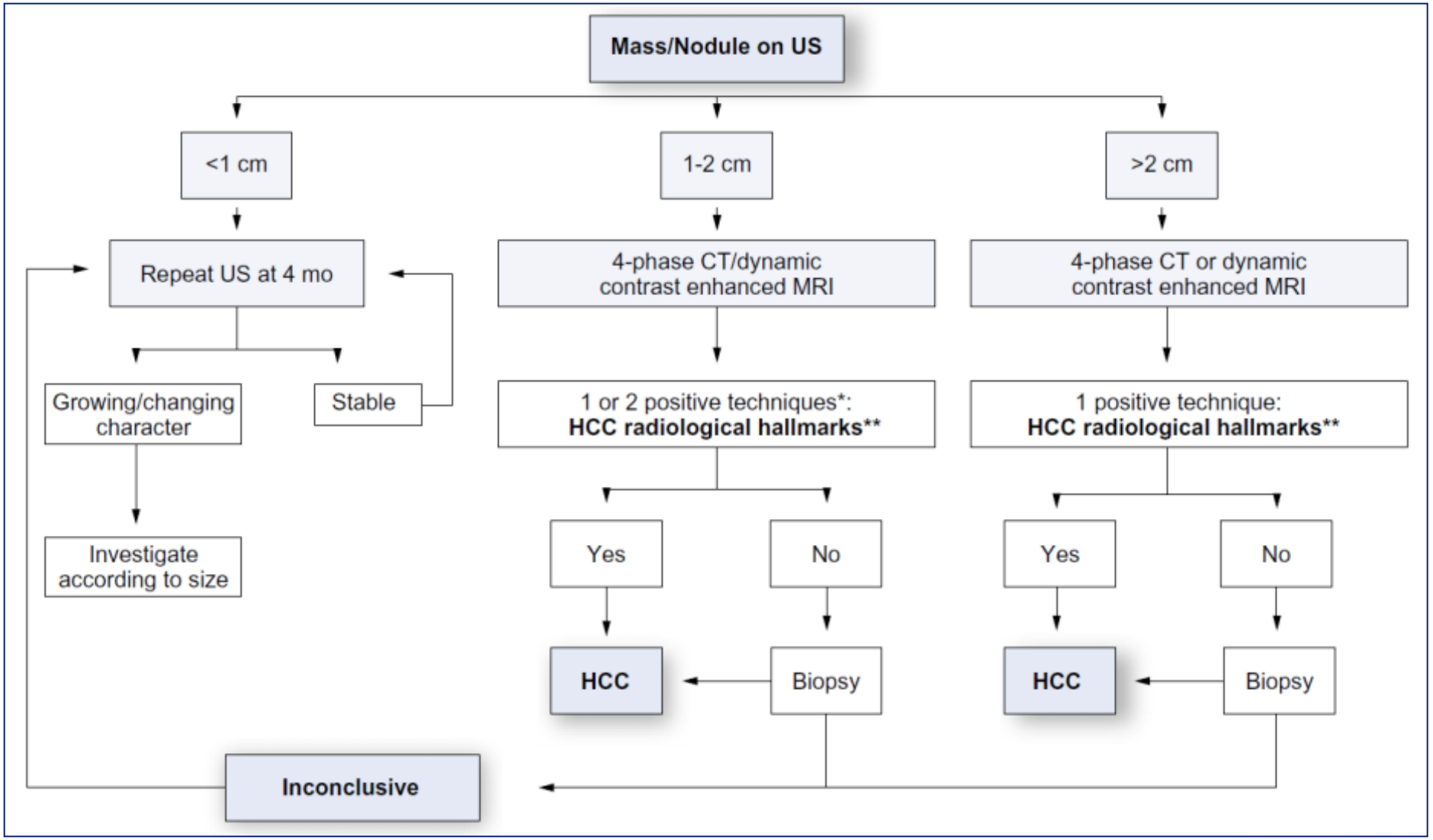
Diagnostic algorithm for HCC



EASL-EORTC Clinical Guidelines, J Hepatology 2012

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HCC Classification Systems

- TNM – neglects underlying liver disease
- Child-Pugh – neglects TNM
- Okuda – (liver disease + % of liver involvement)
- Barcelona Clinic Liver Cancer (BCLC)
- “Royal Free” HCC scoring
- CLIP (Cancer of the Liver Italian Program)
- Japan Integrated Staging (JIS) score
- Hong Kong Liver Cancer (HKLC)
- ITA.LI.CA

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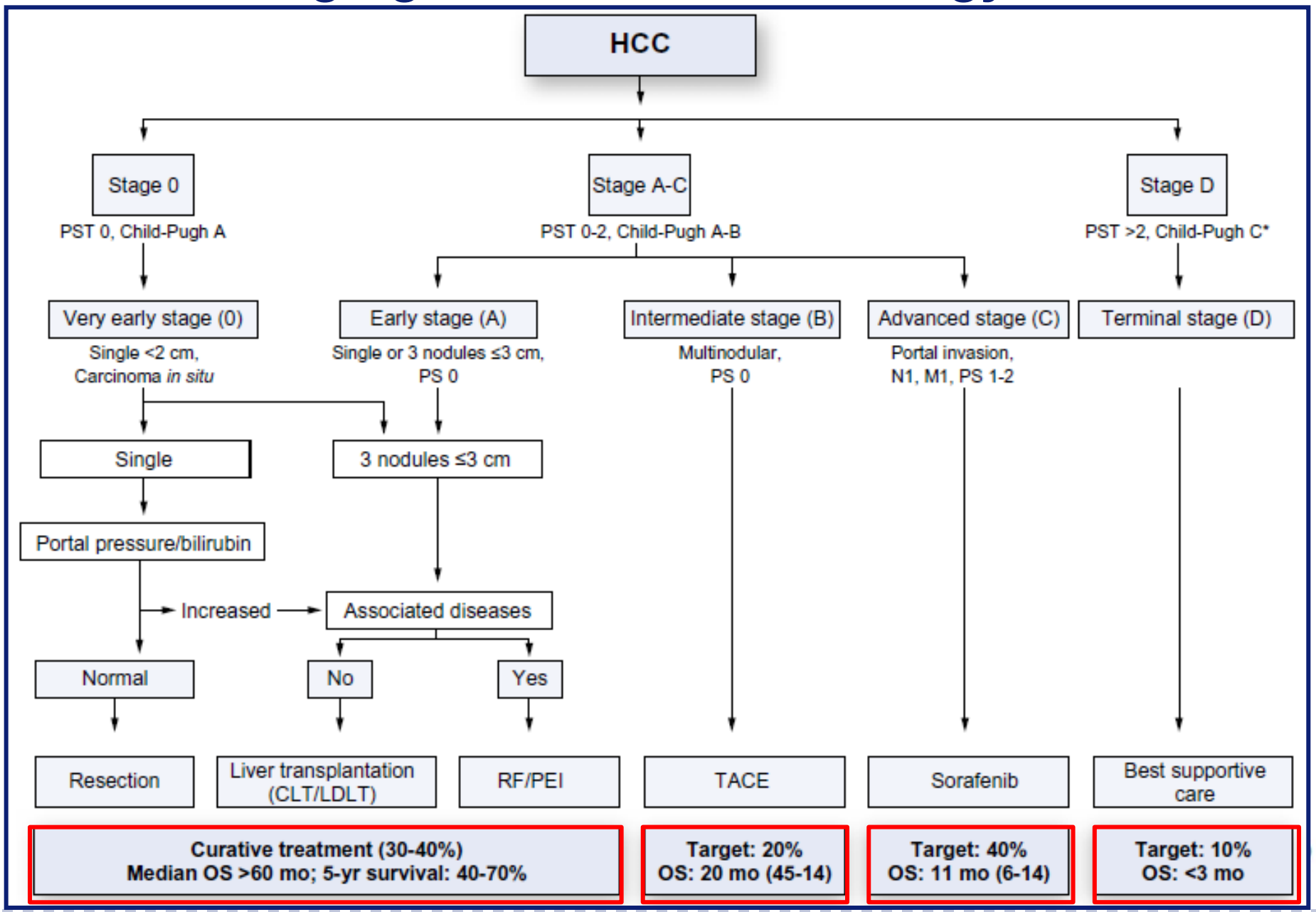
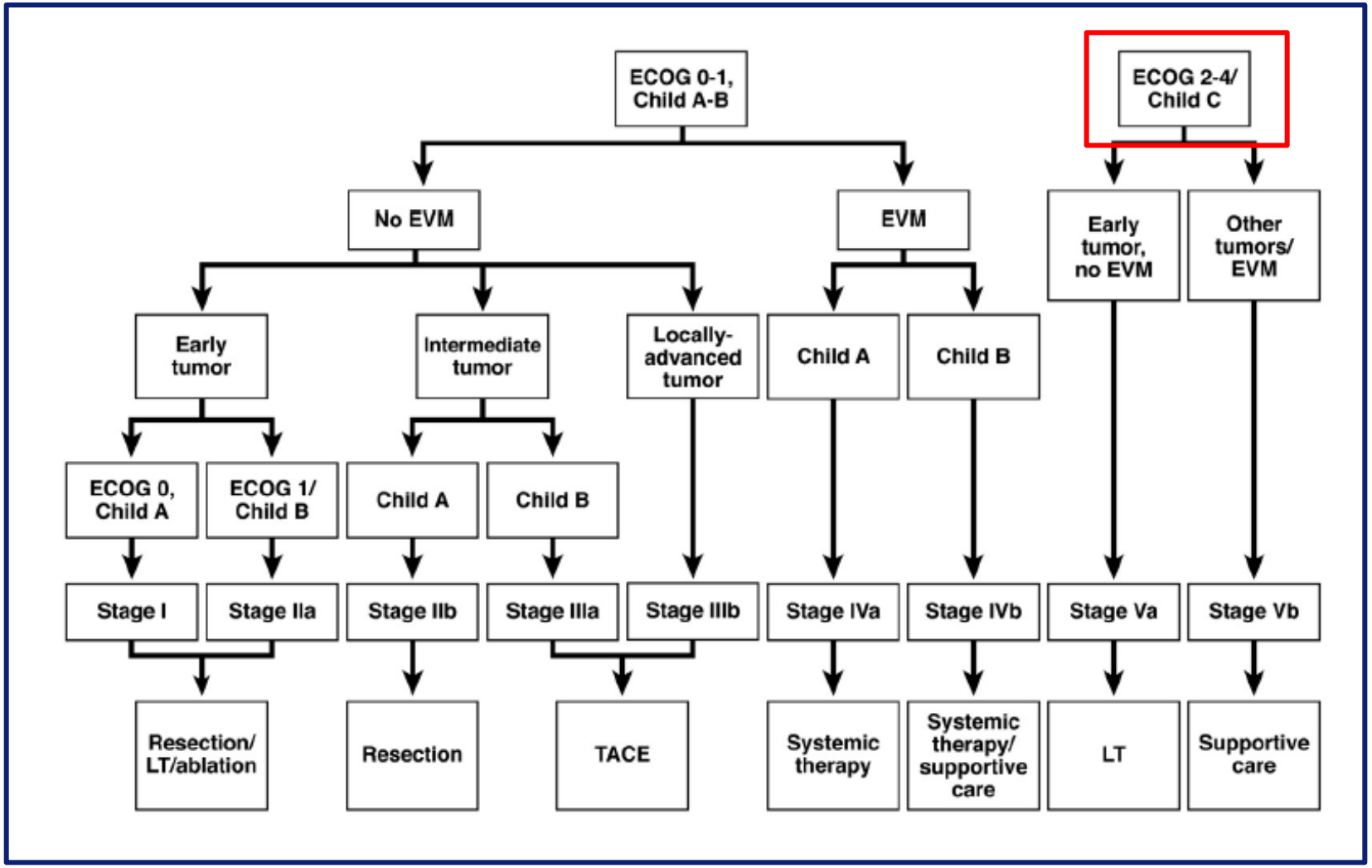
BCLC staging and treatment strategy for HCC



Hong Kong Liver Cancer (HKLC) Staging System



Yau et al. Gastroenterology 2014

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Surgical resection for HCC

- Remains the main pillar in curative treatment of HCC
- Patients **ideally** suited for resection have localized HCC confined to the liver without radiological evidence of invasion of the hepatic vasculature, well preserved hepatic function, and no evidence of portal hypertension
- Thus **only 15-30%** of newly diagnosed patients are potentially **resectable**

Llovet et al. Semin Liver Dis 2005

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Chronic liver disease/cirrhosis - problems

- Deterioration of protein synthesis and metabolism
- Gastrointestinal tract congestion, ascites, pancytopenia due to portal hypertension and hypersplenism
- Susceptibility to infectious disease and hepatopulmonary syndrome (hypoxemia) due to increased shunt vessels
- Lower rate of regeneration

High morbidity and mortality following anesthesia and surgery

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Multidisciplinary approach is necessary!!!

- Due to complexity of disease:

  - tumor stage
  - liver function
  - physical status (co-morbidity)

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Patient evaluation before liver resection

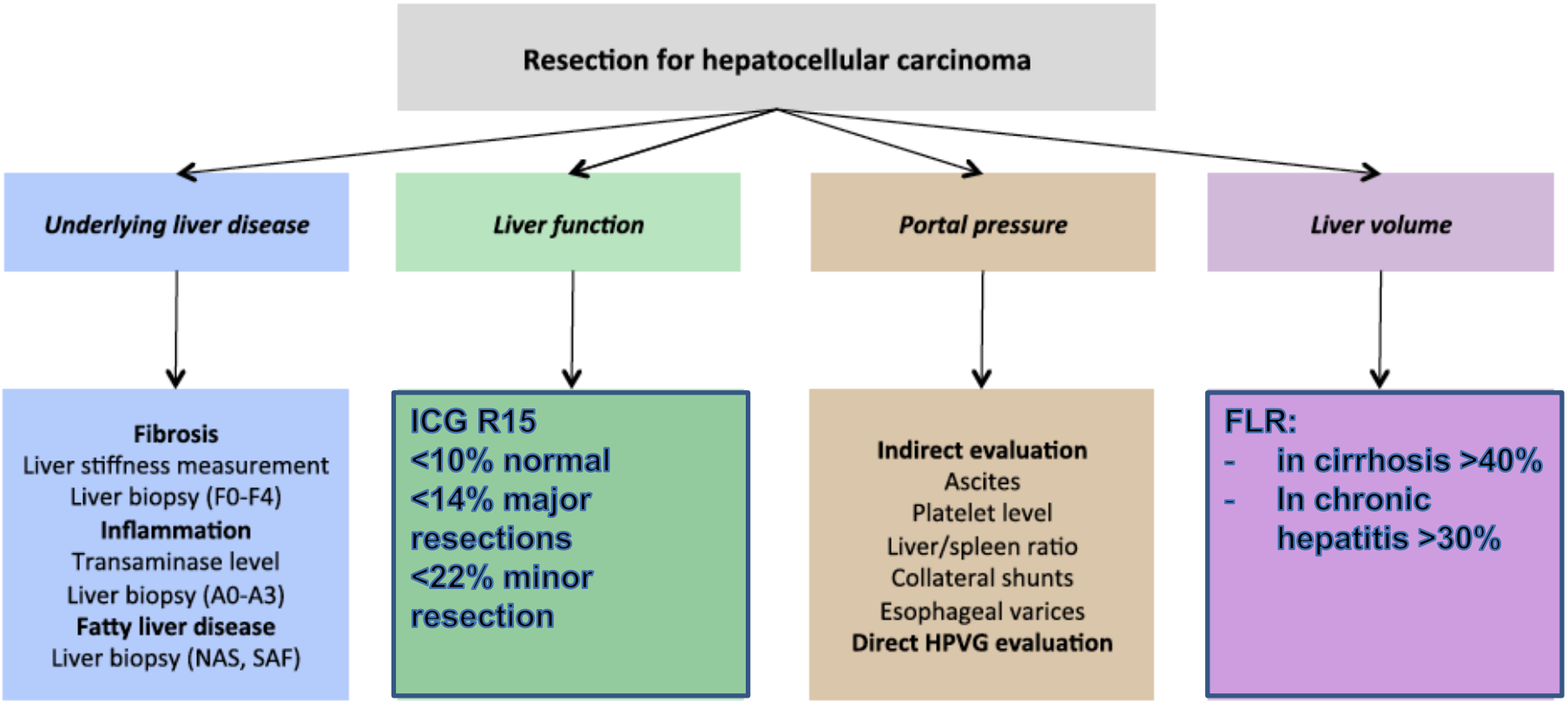

Fig. 1. Evaluation of the underlying parenchyma's status and function. NAS: Non-alcoholic fatty liver disease activity score; SAF: Steatosis, activity, fibrosis; ICG: indocyanine green; PVE: Portal vein embolization; HPVG: Hepatic vein portal vein gradient; CT: Computed tomography; FLR: Future liver remnant; TLV: Total liver volume.

Fan ST J Hepatobiliary Pancreat Sci 2010
Cauchy et al. Best Pract Res Clin Gastroenterol 2014

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Patients selection for resection in chronic liver disease

Resection	Criteria
Minor	Child-Pugh A
	Bilirubin $\leq$ 2 mg/dL
	Absence of ascites
	Platelets >100,000/mm
Major	Criteria for minor resection plus:
	Bilirubin $\leq$ 1 mg/dL
	Absence of portal hypertension
	Portal vein embolization for future liver remnant of <40%

Truty and Vauthey. Ann Surg Oncol 2010

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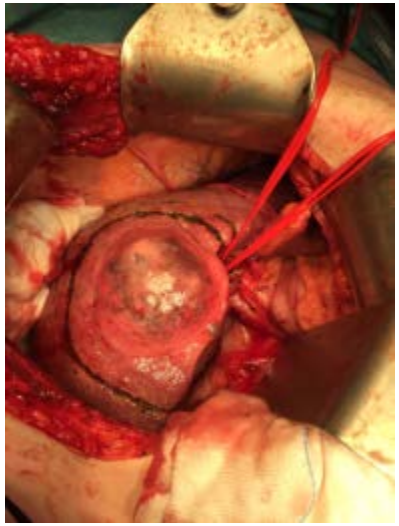
Surgical resection for HCC - important questions

- Tumor size
- Number of tumors
- Anatomic vs non-anatomic resections
- Resection margin
- Presence of portal hypertension
- Ruptured HCC
- Vascular invasion
- Extrahepatic disease



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- 74-year … atitis B
  - Diab… d kidney funct…
  - Liver … 5, bilirubin 11 u… ^{3}
- Referre…

- US elas… d grade 3 fibrosis
- CT volumetry – FLR (segment 2,3,1 – FLR/TLV 25%)

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- PVE – r

- control CT volumetry 4 weeks later: FLR 29%
- extended right hemihepatectomy (right trisectionectomy)

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HCC resection: tumor size

- size per se is not contraindication for resection, however the size reflects the risk of microvascular invasion and therefore poor outcome

  - <2 cm - 20% MVI
  - 2-5 cm - 30-60% MVI
  - >5 cm - 60-90% MVI

- large tumors (>5 cm) often require major hepatectomy

Ng et al. Ann Surg Oncol 2005
Llovet et al Semin Liv Dis 2005

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HCC resection: tumor size >5 cm

- role of portal vein embolization (PVE) if future liver remnant is <40-50%
  - morbidity and mortality rate of 2,2% and 0%
  - impaired regeneration in cirrhotic liver (9% vs 16%)
- mortality after major resection up to 10%
- 5-year survival 30-35%
- risk factors for impaired long-term survival:
  - macroscopic vascular invasion
  - multiple lesions
  - underlying cirrhosis

Farges et al. Ann Surg 2003
Abulkhir et al. Ann Surg 2008
Cauchy et al. Best Pract Res Clin Gastroenterol 2014

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Early HCC (<2 cm): resection or ablation?

Table 1 Are ablation and resection comparable for treatment of early hepatocellular carcinoma?

	Radiofrequency ablation	Liver resection
No of patients	218 (5 centers)	132 (2 centers)
Perioperative mortality	0%	0.8%
Sustained complete response	97.2%	100%
5-year overall survival rate	55%	70%
5-year recurrence rate	80%	68%

Arii S et al. Hepatology 2000
Roayaie et al. Hepatology 2013
Majno et al. Hepatology 2010
Mazzaferro et al. Semin Liver Dis 2014

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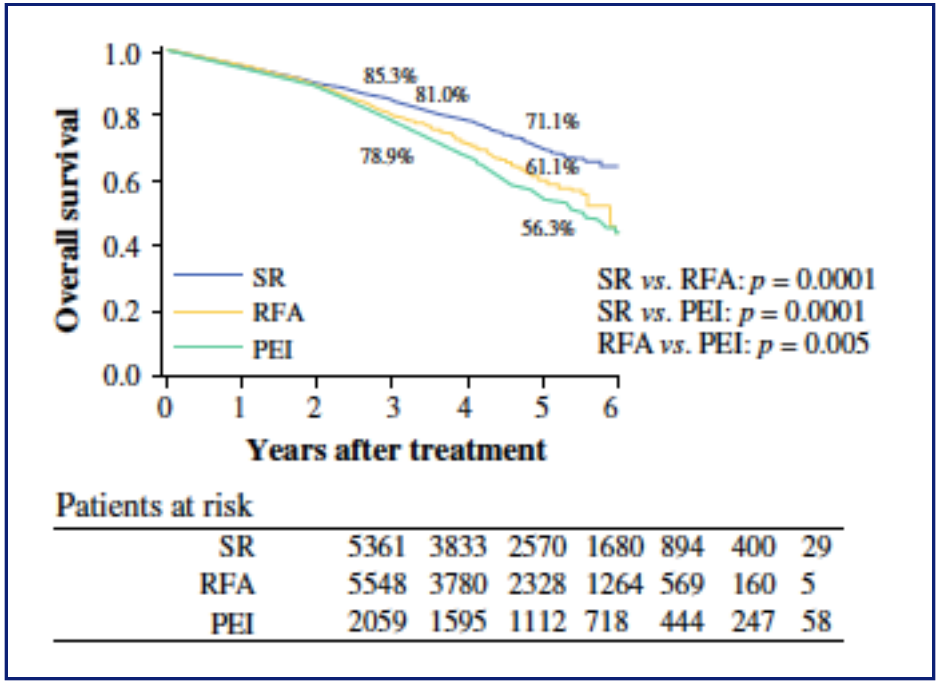
Resection versus ablation for HCC



Patients at risk

SR	5361	3833	2570	1680	894	400	29
RFA	5548	3780	2328	1264	569	160	5
PEI	2059	1595	1112	718	444	247	58

Hasegawa et al. Ann Surg Oncol 2014

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HCC resection: number of tumors

- multiple HCCs has been traditionally considered as contraindication for surgical resection due to the high recurrence rate (5-year disease-free survival of 10%) and lower 5-year survival
- however in selected cases surgical resection can offer better survival then TACE – in some series up to 39-58% (especially if tumors are within Milan criteria in patients not suitable for liver transplantation)

Ng et al. Ann Surg Oncol 2005
Ishizawa T Gastroenterology 2008
Yin et al. J Hepatol 2014

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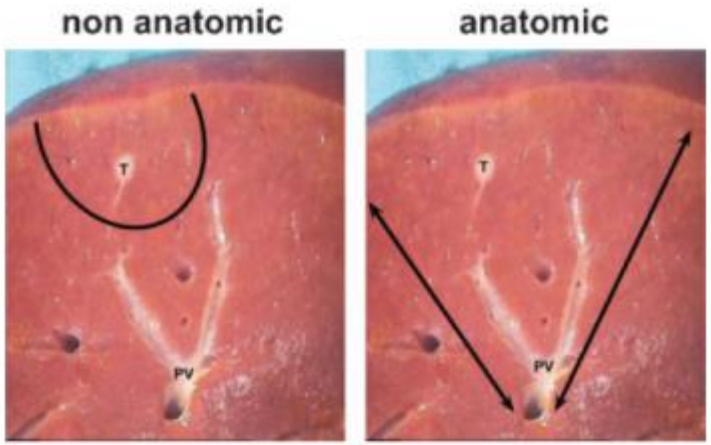
HCC resection
- Anatomic vs Non-anatomic

- HCC spreads and metastasizes via portal venous system
- anatomical resections can reduce local recurrence without the increased operative risk, especially in tumors between 2 and 5 cm



Eguchi et al. Surgery 2008
Yin et al. J Hepatol 2014
Mazzaferro et al. Semin Liver Dis 2014
Shidoh et al. J Hepatol 2016

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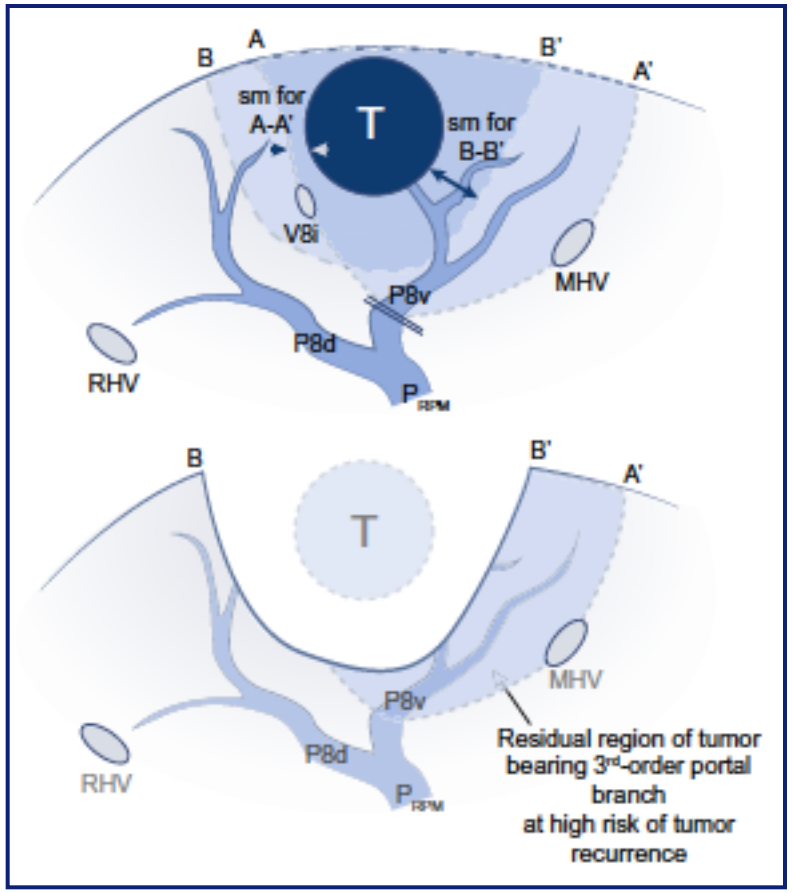
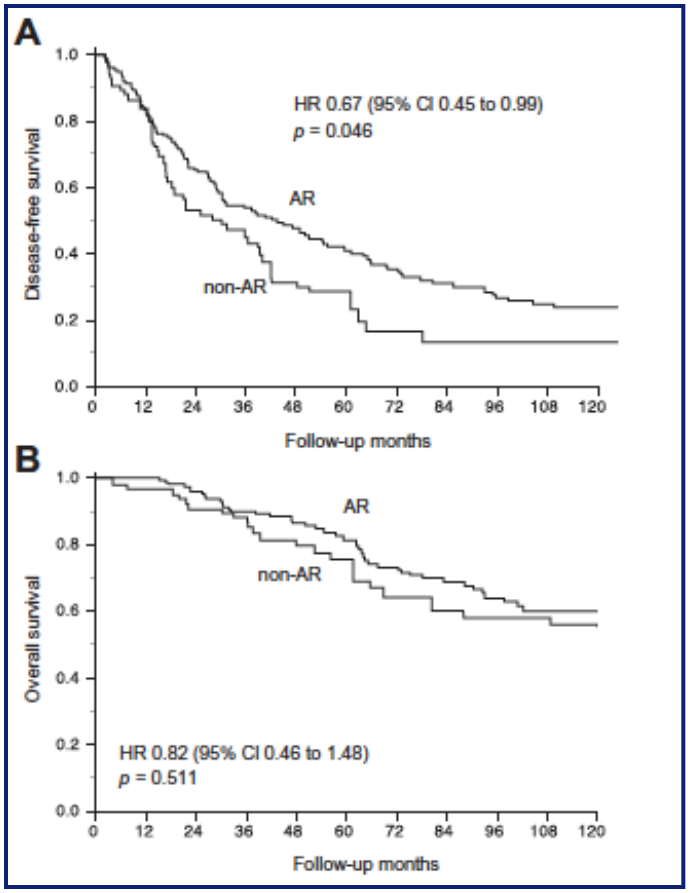
HCC resection
- Anatomic vs Non-anatomic





Shidoh et al. J Hepatol 2016

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HCC resection: margin

World J Surg (2016) 40:1429–1439
DOI 10.1007/s00268-016-3421-5

World Journal of Surgery

CrossMark

ORIGINAL SCIENTIFIC REPORT

Anatomical Resection But Not Surgical Margin Width Influence Survival Following Resection for HCC, A Propensity Score Analysis

Jung-Woo Lee[3] · Young-Joo Lee[2] · Kwang-Min Park[1] · Dae-Wook Hwang[1] · Jae Hoon Lee[1] · Ki Byung Song[1]

Shi et al. Ann Surg Oncol 2007
Tang et al. Hepatogastroenterology 2012
Lee et al. World J Surg 2016

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HCC resection: portal hypertension

Differences in assessment of portal hypertension:

- direct measurements (transjugular HVPG – PH if HVPG >10 mm Hg)
- non invasive:
  - CT-based liver/spleen volume ratio
  - surrogate markers of portal hypertension (esophageal varices, splenomegaly and **platelets count below 100 000/mm^3)**

Bruix et al. Gastroenterology 1996
Cucchetti et al Ann Surg Oncol 2009

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HCC resection: portal hypertension

- major resections (>3 segments) in patients with portal hypertension are associated with 50% mortality
- minor resections should be cautiously evaluated (high complications rate – postoperative liver failure)

Boleslawski et al. BJS 2012
Iranmanesh et. Al J Hepatol 2014

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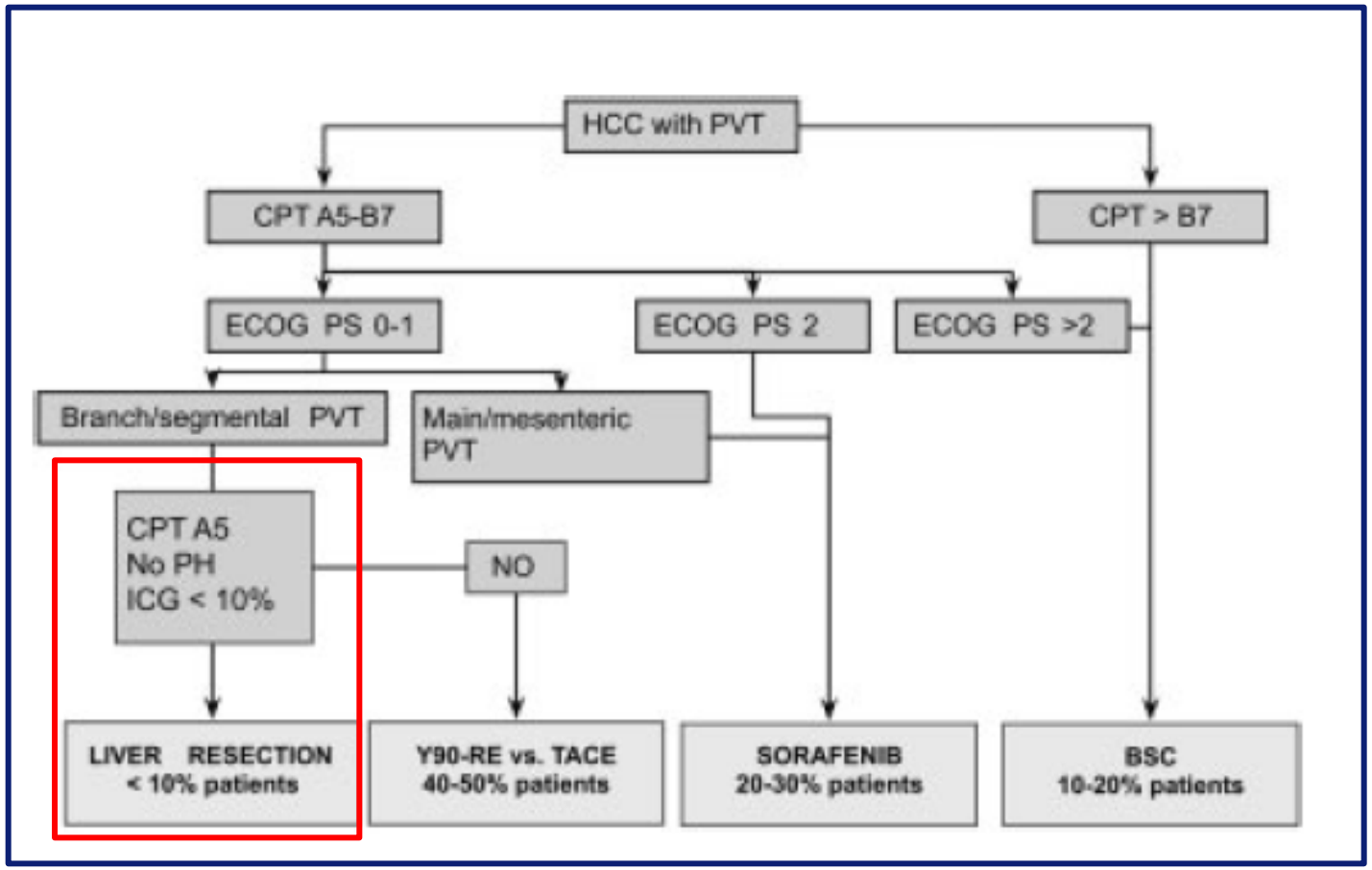
Management of HCC with portal vein thrombosis



Mazzaferro et al. Semin Liver Dis 2014

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HCC resection: vascular invasion

- invasion of portal trunk, hepatic veins or vena cava is associated with poor outcome
- in selected patients (normal liver function + excellent general status) resections combined with tumor thrombus removal can provide favorable results

Inoue et al. Surgery 2009
Shi et al. Ann Surg Oncol 2010
Kokudo et al. J Hepatol 2014

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HCC resection and tumor rupture

- spontaneous rupture of HCC ranges between 5% and 15%
- transarterial embolization is a first line treatment to achieve hemostasis
- liver resection is an option if negative surgical

Management of ruptured hepatocellular carcinoma in a European tertiary care center

Vincent Rijckborst[a], Martijn J. ter Borg[e], Eric T. Tjwa[a], Dave Sprengers[a], Kees Verhoef[d], Adriaan Moelker[b], Jan N. Ijzermans[c] and Robert A. de Man[a]

Lymph node dissection for HCC

- Lymph node dissection during liver resection for HCC remains controversial
- In the recent systematic review:
  - prevalence of lymph node dissection was 52%
  - incidence of lymph node metastasis (LNM) was 44.5%
  - 3- and 5-year survival in patients with LNM was 27.5% and 20.8% compared to 60.2% and 42.6% in patients without LNM

Amini et al. J Gastrointest Surg 2014

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HCC resection: extrahepatic disease

- diaphragmatic involvement
  - infrequent
  - recommended en-bloc resection
- adrenal gland metastasis – adrenalectomy can be recommended in patient without or with well-controlled intrahepatic disease
- peritoneal metastases – in very selected patients, scarce data

Yamashita et al. Surg Today 2011
Chua et al. Surgical Oncology 2012

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Technical consideration in liver resection for HCC

- Laparoscopic liver resection
- Portal clamping (Pringle)
- Anterior approach
- Parenchyma transection
- ALPPS

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Laparoscopic vs open liver resection for HCC

- Systematic review of 10 studies reported on 494 patients – 213 laparoscopic liver resection and 281 open liver resection for HCC.
  - lesser blood loss and blood transfusion requirements
  - lesser overall morbidity including decompensation of liver cirrhosis
  - shorter length of stay
  - no differences in oncological outcomes (margin and survival)

Zhou et al. Dig Dis Sci 2011

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Laparoscopic vs open liver resection for HCC

- French multicenter study on 351 patients showed similar results;
- However:

Table 2 Operative data in 351 patients submitted to laparoscopic liver resection for hepatocellular carcinoma

Operative data	Value
Type of laparoscopic main liver resection, *n* (%)	
Major hepatectomy	36 (10%)
Right hepatectomy	20 (6%)
Left hepatectomy	14 (4%)
Central hepatectomy	2 (0.5%)
Left lateral sectionectomy, *n* (%)	92 (26%)
Segmentectomy, *n* (%)	83 (24%)
Wedge resection, *n* (%)	140 (40%)

- 90% minor resections
- data from 1998-2010
- no randomized studies

Soubrane et al. HPB 2013

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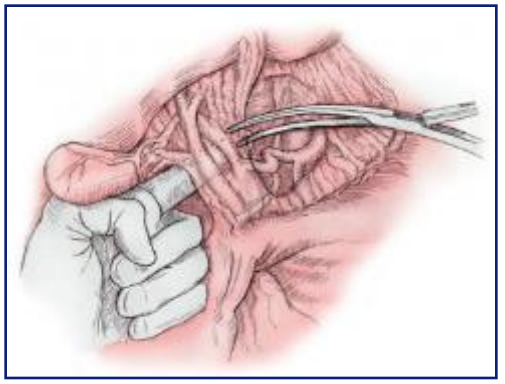
Portal clamping during resection of HCC



- Intermittent or continuous?
- In the systematic review and meta-analysis no advantage of the standard use of portal clampig

Rahbari et al. BJS 2008

- However, in two recent studies portal clamping was associated with:
  - lower overall patient survival
  - early recurrence

Hao et al. Surg Today 2016
Wang et al. Ann Surg Oncol 2009

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Parenchyma transection in cirrhotic liver

- In the Cochrane review there were no differences between the techniques, however Kellyclasie was the quickest and most cost-efficient

Garusamy et al. Cochrane Database Syst Rev 2009

- Depends on the preference, skills and experience of the operating surgeon

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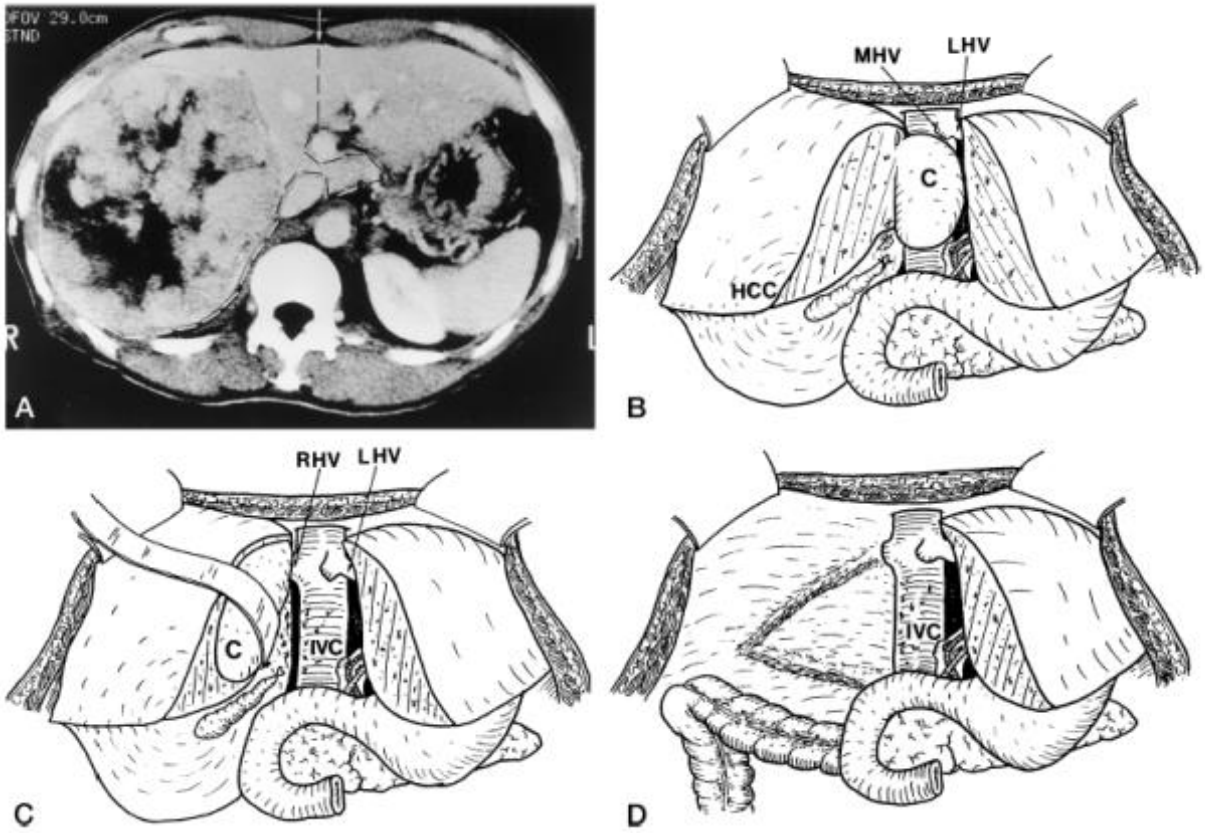
Anterior approach in HCC



- Proposed by group from Hong Kong in case of large HCC in the right hemiliver

Liu et al. Ann Surg 2000

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Anterior approach in HCC

- The same group showed in the randomized controlled trial that anterior approach in HCC >5 cm was associated with:
  - lower transfusion requirements
  - lower number of patients requiring transfusions
  - better overall survival (but not disease free survival)

Liu et al. Ann Surg 2006

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The use of ALPPS in HCC

fivefold higher 90-days mortality of 31% (*7% CLRM*)

- age >61 years was the risk factor for mortality

D'Haese et al. Ann Surg Oncol 2016

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Outcome after surgical resections for HCC

- 5-year survival of **60-80%**
- peri-operative mortality of **2-3%**

  - drop from 15% in 1980’ (!)

- blood transfusion requirement **less than 10%**

  - drop from 80-90% in the last two decades (!)

Poon et al. Ann Surg 2002
Makuuchi et al. Liver Transpl 2004
Llovet JM, Bruix J. J Hepatolo 2008

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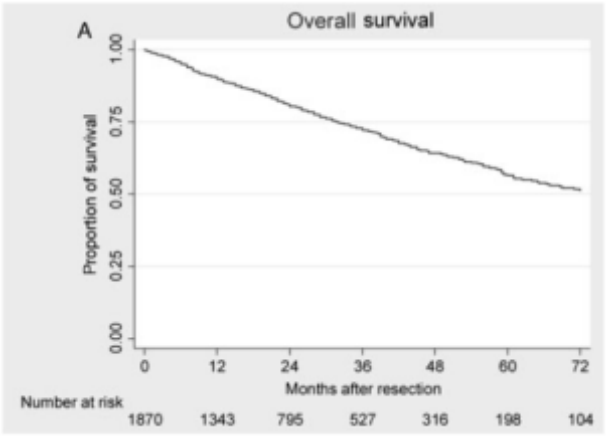
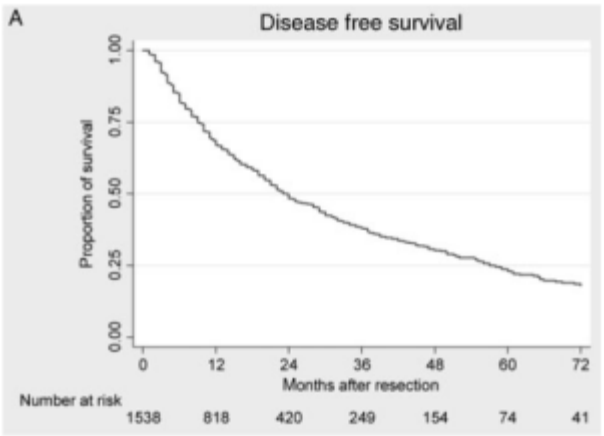
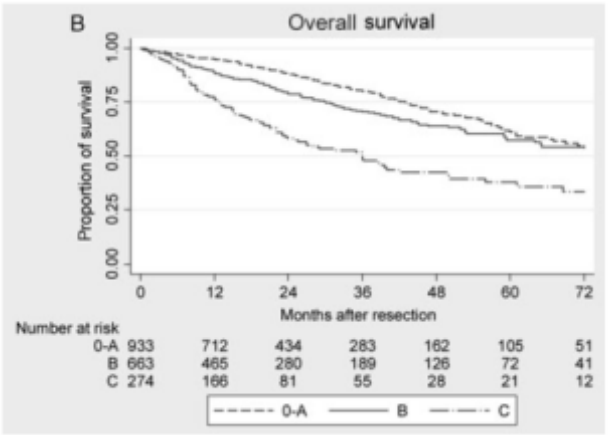
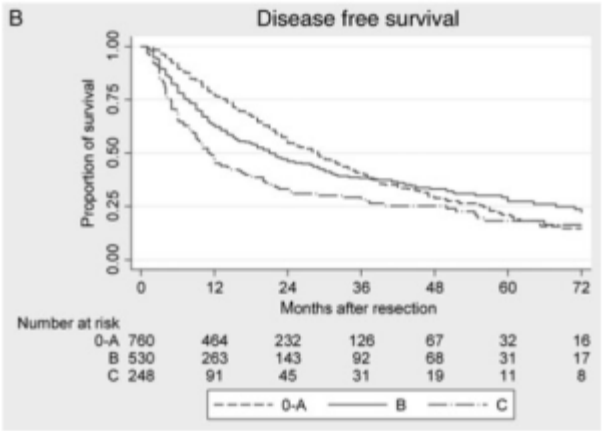
Outcome after surgical resections for HCC

- **up to 70-80%** recurrence within 5 years (both intrahepatic metastases and de novo tumors)









Torzilli et al. Ann Surg 2013

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Risk factors for overall survival and for recurrence after resection

Overall survival

- ✓ Macrovascular invasion
- ✓ Tumor size >5 cm
- ✓ Preoperative bilirubin
- ✓ Esophageal varices
- ✓ Cirrhosis

Recurrence

- ✓ Microvascular invasion
- ✓ Poor histological differentiation
- ✓ Satellites
- ✓ Multifocal disease

Torzilli et al. Ann Surg 2013

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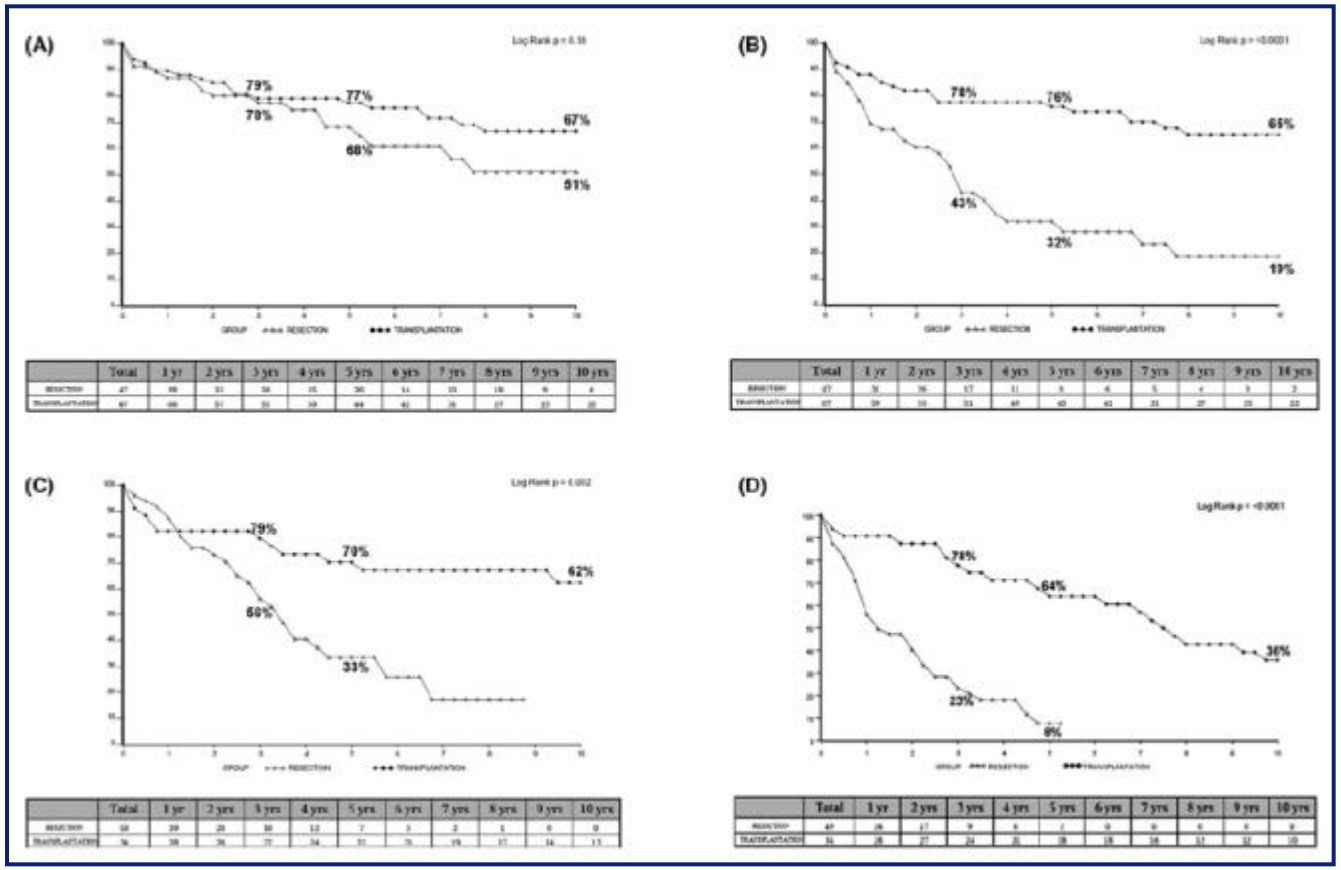
Resection vs transplantation for HCC

<3 cm

>3 cm



- liver transplantation is associated with the best outcome for early HCC

Adam et al. Ann Surg 2012

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Resection vs liver transplantation for HCC

- however:

  - limited organ availability

  - lifelong immunosuppression after liver transplantation

- liver resection for early HCC as first line treatment with curative intention and **salvage liver transplantation** in cases of HCC recurrence → better selection of patients for liver transplantation

Majno et al. Hepatology 2000
Poon et al. Ann Surg 2002

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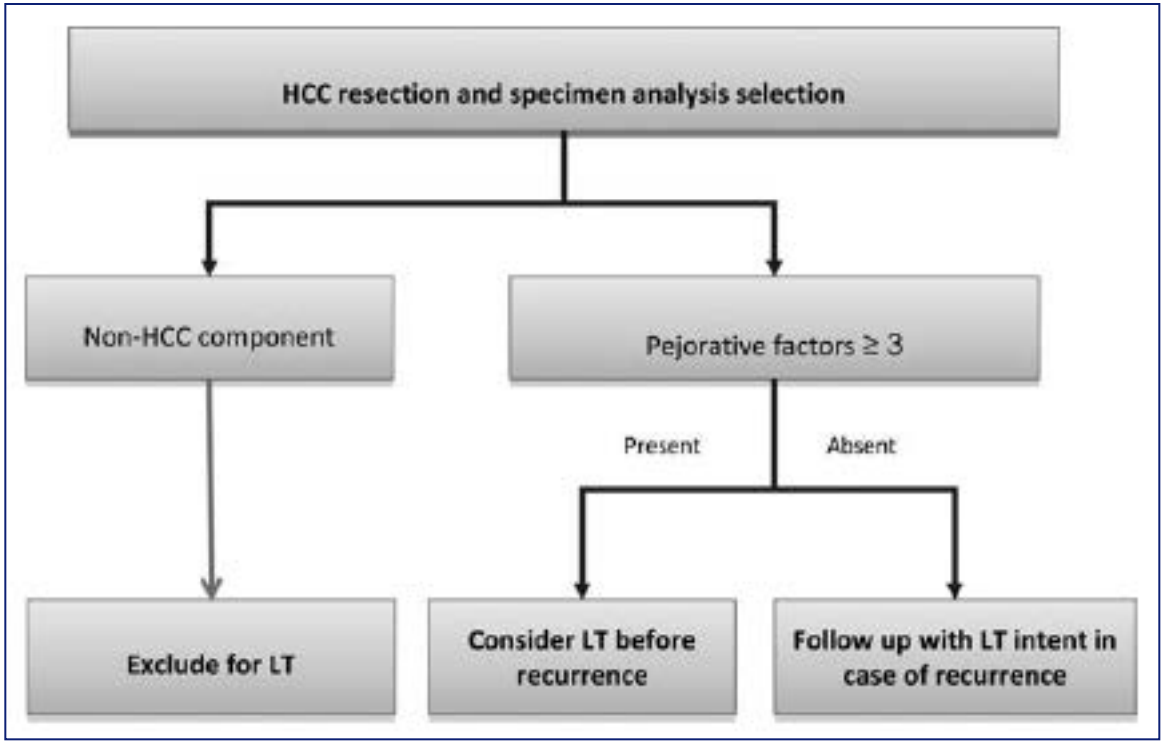
Resection vs liver transplantation for HCC



- risk factors: presence of cirrhosis, diameter >3 cm, microscopic vascular invasion, satellite nodules and poor differentiation

Fuks et al. Hepatology 2012
Sapisochin et al. Ann Surg Oncol 2013
Ferrer-Fabrega et al. Hepatology 2016

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Conclusions

- Resection is a first-line treatment option for HCC in patients with solitary tumor and very well preserved liver function (Child-Pugh A)
- Multidisciplinary approach is necessary in patients with HCC in cirrhotic liver
- 5-year survival of 60-80% can be achieved after liver resection with peri-operative mortality of 2-3%
- Recurrence rate after liver resection is as high as 70% at 5 year

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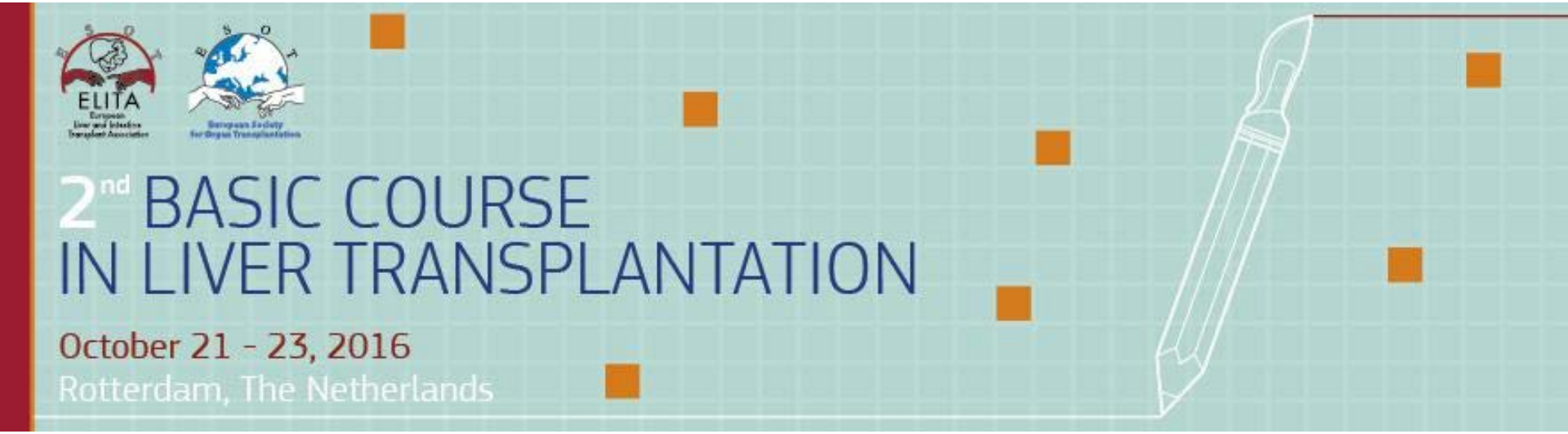
SAVE THE DATE 21-23 OCTOBER 2016 in Rotterdam



Thank you for your attention

Questions?

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