The Cirrhotic Patient with Multiple Small (< 2 cm) Hepatic Nodules

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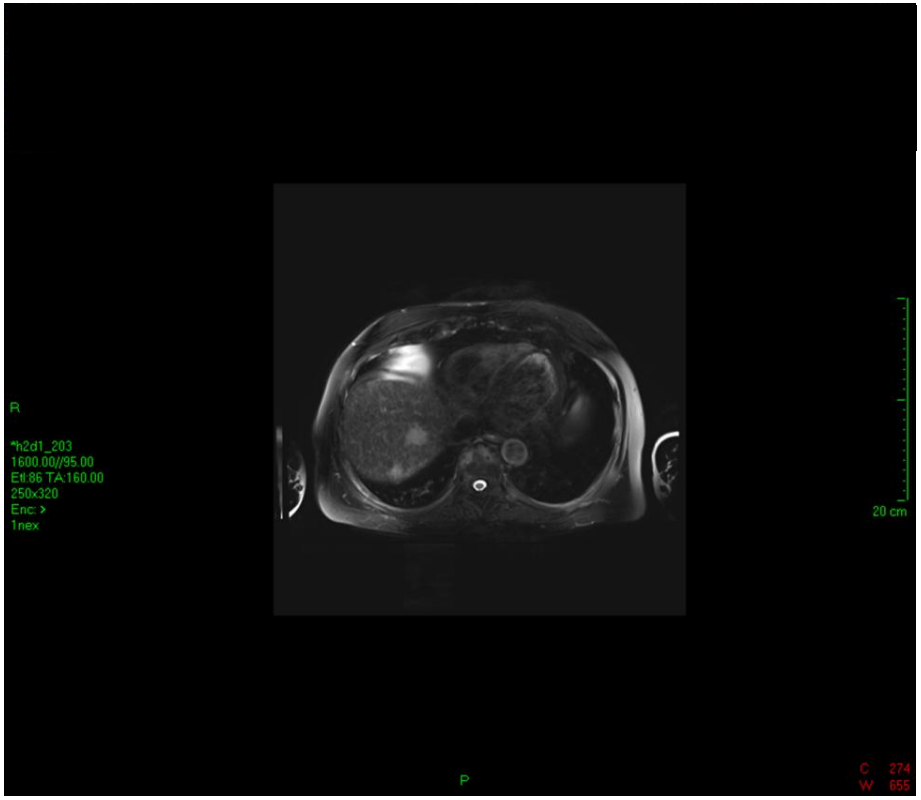
Case

- 48 year-old male born in Ethiopia

- Hepatitis B and D cirrhosis
- Liver biopsy 2009:

  Fibrosis stage 3; Focal hepatocyte dysplasia
- US - Multiple small hyper-echoic nodules
- CT – Multiple small hypodense nodules (< 1 cm) some with arterial enhancement

MRI-T2W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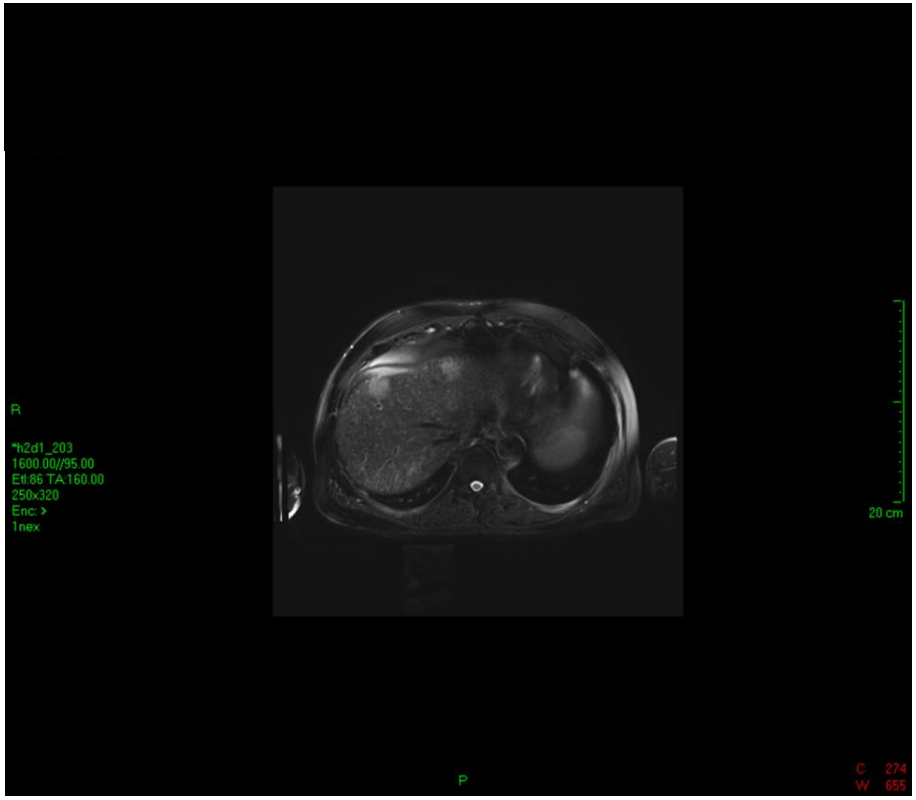
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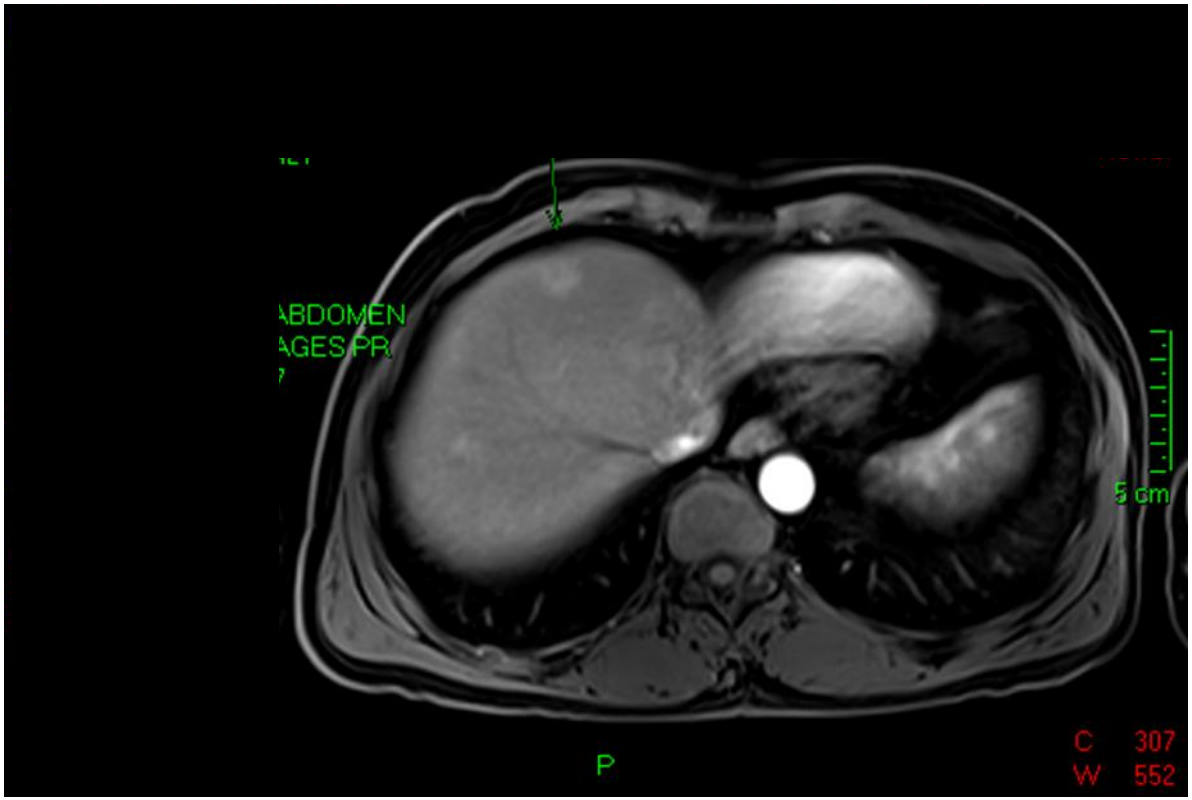
MRI-T1W-Arterial Phase



No portal venous or late phase ‘‘wash-out’’ were demonstrated

Cirrhosis

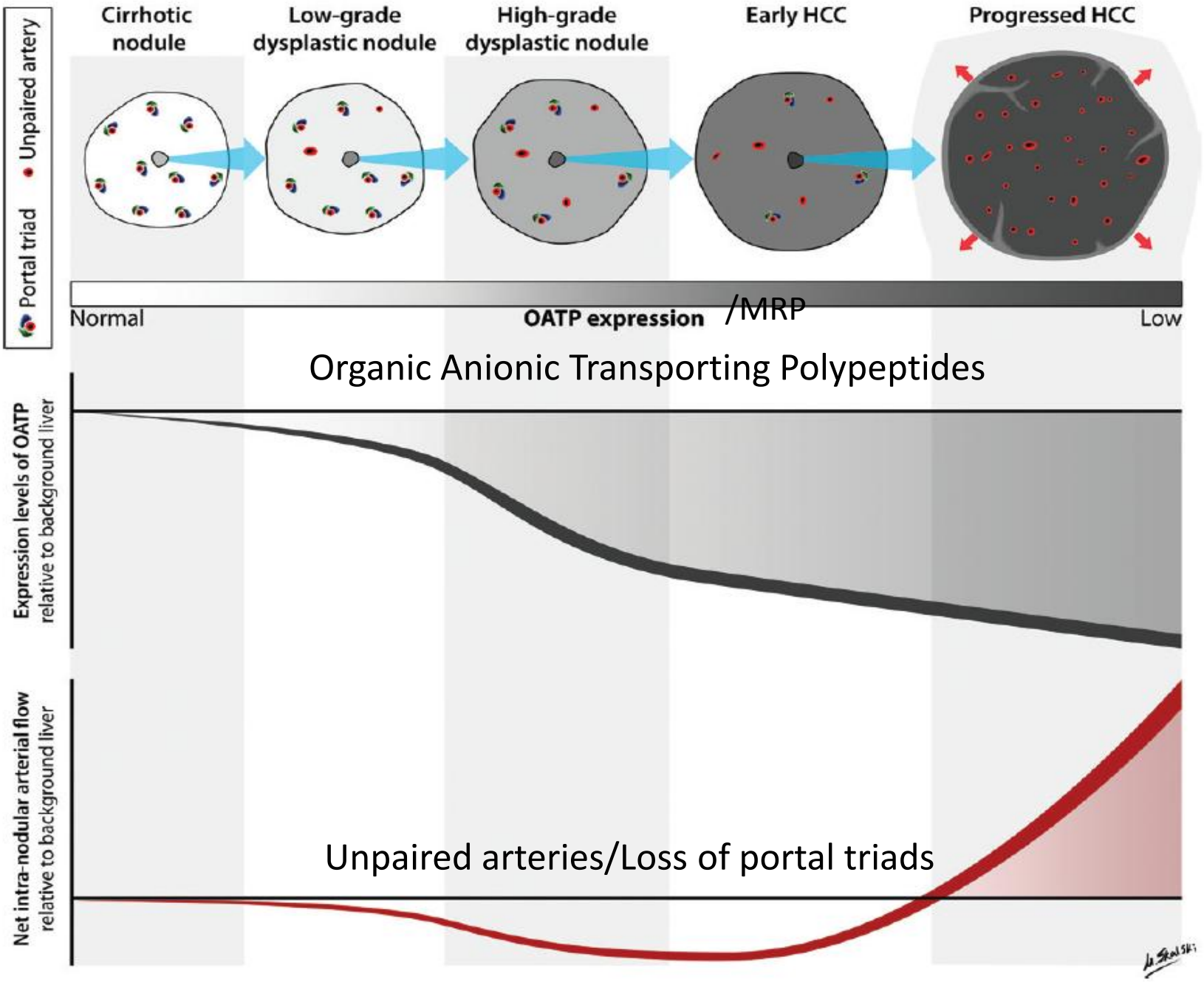
- Child-Pugh class A-5
- No esophageal varices
- Bilirubin=0.5 mg/dl
- Alfa-fetoprotein=2.9 ng/ml

Small (< 2 cm) Hepatic Nodules

- Regenerative nodule
- Dysplastic nodule (Low/high grade)
- Early hepatocellular carcinoma (HCC) – Multiple
- Arterio-portal shunts
- Other

Diagnosis

- MRI - Liver-specific agents
- Lipiodol angiography
- FDG^{18}
- Per-cutaneous biopsy – Markers of HCC
- Laparascopic biopsy


Portal triad
Unpaired artery
Cirrhotic nodule
Low-grade dysplastic nodule
High-grade dysplastic nodule
Early HCC
Progressed HCC
Normal
OATP expression /MRP
Low
Organic Anionic Transporting Polypeptides
Expression levels of OATP relative to background liver
Net intra-nodular arterial flow relative to background liver
Unpaired arteries/Loss of portal triads

MRI and Liver-Specific Contrast Agents

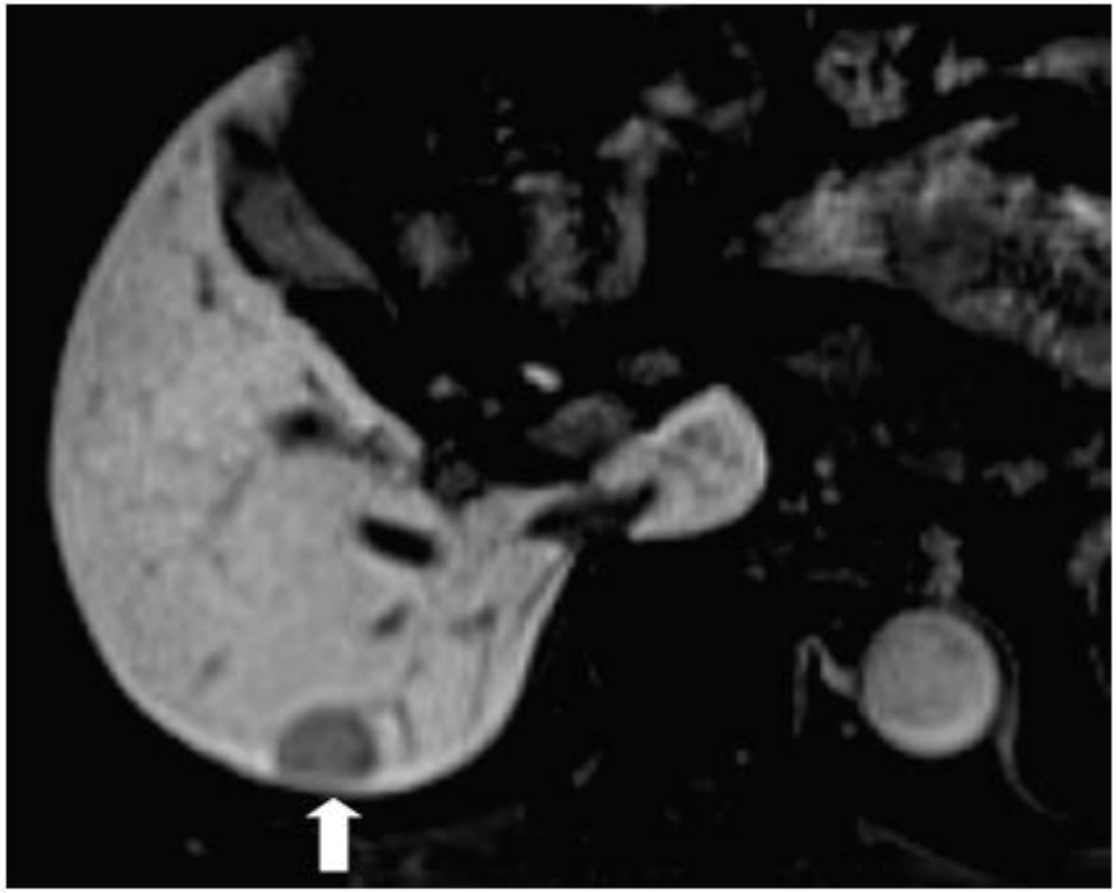
- Characteristic features of HCC:
  - Arterial hyper-vascularity
  - Venous and/or late dynamic phases “wash-out”

- In nodules 20 mm or smaller, the sensitivity of MRI is only 62%
  - Early HCCs often are not hyper-vascular and have persistent portal venous blood supply

MRI and Liver-Specific Contrast Agents

- Liver-specific contrast agents:
  - Are taken-up by hepatocytes
  - Provide information regarding hepatocyte presence and function in the delayed hepatobiliary phase
- Gadoxetate (Primovist) has been the liver-specific contrast agent most thoroughly investigated
- During the hepatobiliary phase most HCCs, including early HCC, appear hypo-intense

HCC appearing hypo-intense during the hepatobiliary phase



MRI and Liver-Specific Contrast Agents

- Enhanced MRI imaging appears useful for differentiation of small HCCs from dysplastic nodules
- A variable proportion of high-grade dysplastic nodules will begin to show lack of uptake of gadoxetate, resulting in overlap with early HCCs
- From a practical standpoint:
  - Follow-up the nodules with interval imaging if they are smaller than 1.5 cm
  - A biopsy may be advocated if lesions are larger than 1.5 cm

Hepatocellular Carcinoma - Biopsy

- Sensitivity of liver biopsy ranges between 70% and 90% for all tumor sizes
- Pathological diagnosis is particularly complex for nodules between 1 and 2 cm
- First biopsy was reported positive in 60% of cases for tumors less than 2 cm

Hepatocellular Carcinoma - Biopsy

- Morphological criteria alone still pose problems for the differential diagnosis of high-grade dysplastic nodules versus early HCC
- Combinations of different protein markers:

  HSP70, GPC3, and GS – performed acceptably:

  Sensitivity and specificity of 72% and 100%, respectively

Progression Rate of Dysplastic and Regenerative Nodules to HCC

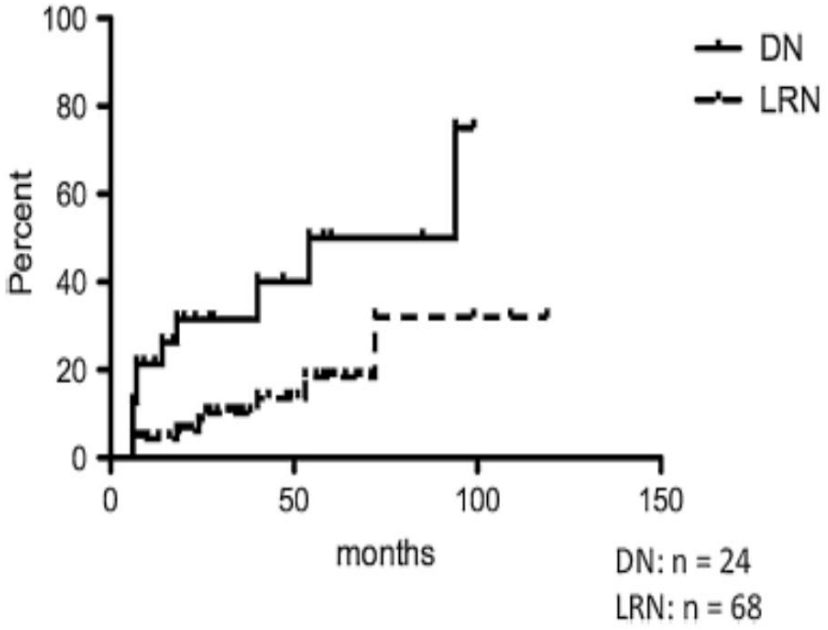


Table 4 Occurrence cases of new HCC lesions remote from the nodules

Parameter	LRN	DN	*p* value
Occurrence of new HCC (+)	9	5	0.4100
Occurrence of new HCC (−)	51	17	

Sato T, et al. Hepatol Int 2015

Multiple Occurrence of Borderline Hepatocellular (Dysplastic) Nodules and HCC

	Cirrhotic livers with multiple BHNs	Cirrhotic livers with single BHN	*P*
Age	64.5±7.6	61.7±5.6	NS
Sex (M:F)	8:2	12:8	NS
Mean No. of BHN	3.5	1	
Cases with BHN with malignant foci	6/10 (60%)	4/20 (20%)	<0.05
BHN with malingant foci	14/35 (40%)	4/20 (20%)	NS
Association with HCC	8/10 (80%)	3/20 (15%)	<0.01

BHN-Borderline Hepatocellular (Dysplastic) Nodules

Terada T, Nakanuma Y. Virchows Arch 1995

Treatment of Dysplastic Nodules

- Differentiation between high-grade dysplastic nodule from early HCC is so challenging
  - So should we also treat DN?
- In colorectal cancer treatment of precancerous lesions is recommended
- The early treatment of HG-DN might theoretically also improve survival

Simulation model of dysplastic nodule ablation vs. regular follow-up and timely treatment

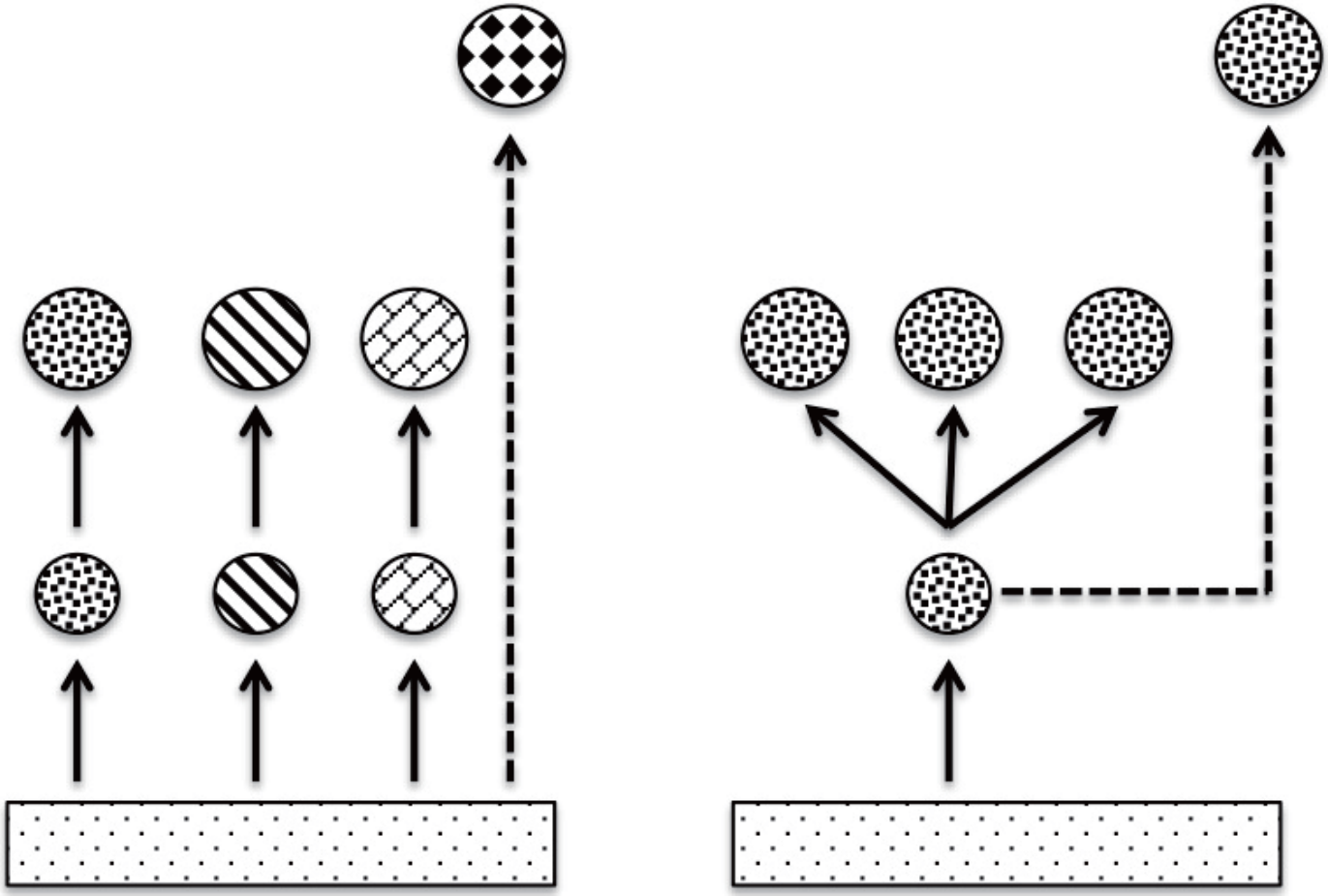
Table 3. Expected Additional 5-Year and 10-Year Overall Survival Benefits of Immediate Treatment of High-Grade Dysplastic Nodule (HGDN) by Radiofrequency Ablation (RFA) (Group I), as Compared with Regular Follow-up and Timely Treatment by Resection (Group II)

	Overall 5-Year Malignant Transformation Rate		
	20%	50%	80%
Risks and benefits in terms of 5-year overall survival			
Increased mortality in Group I due to overtreatment by RFA	0.18%	0.13%	0.07%
Increased procedure-related mortality in Group II	0.13%	0.33%	0.54%
Additional 5-year overall survival benefit of Group I compared with Group II	-0.05%	0.20%	0.47%
Risks and benefits in terms of 10-year overall survival			
Increased mortality in Group I due to overtreatment by RFA	0.16%	0.10%	0.05%
Increased procedure-related mortality in Group II	0.19%	0.43%	0.60%
Additional 10-year overall survival benefit of Group I compared with Group II	0.03%	0.33%	0.55%

- The longer and unpredictable natural history of precancerous lesions of the liver seems to discourage their systematic treatment

Cho YK, et al. Hepatology 2011

Multiple Hepatocellular Carcinoma



Multi-centric occurrence (MO-HCC) – Poly-clonal

Intrahepatic metastasis (IM-HCC) – Mono-clonal

Multiple Hepatocellular Carcinoma

- IM-HCC:
  - Is characterized by an aggressive biological behavior
  - Seems to recur early following surgical resection and
  - Carries a grim prognosis

- MO-HCC:
  - Postsurgical recurrence of may respond well to additional surgery or loco-regional therapy –

    Limited only by hepatic functional reserve

Differentiation of MO-HCC and IM-HCC

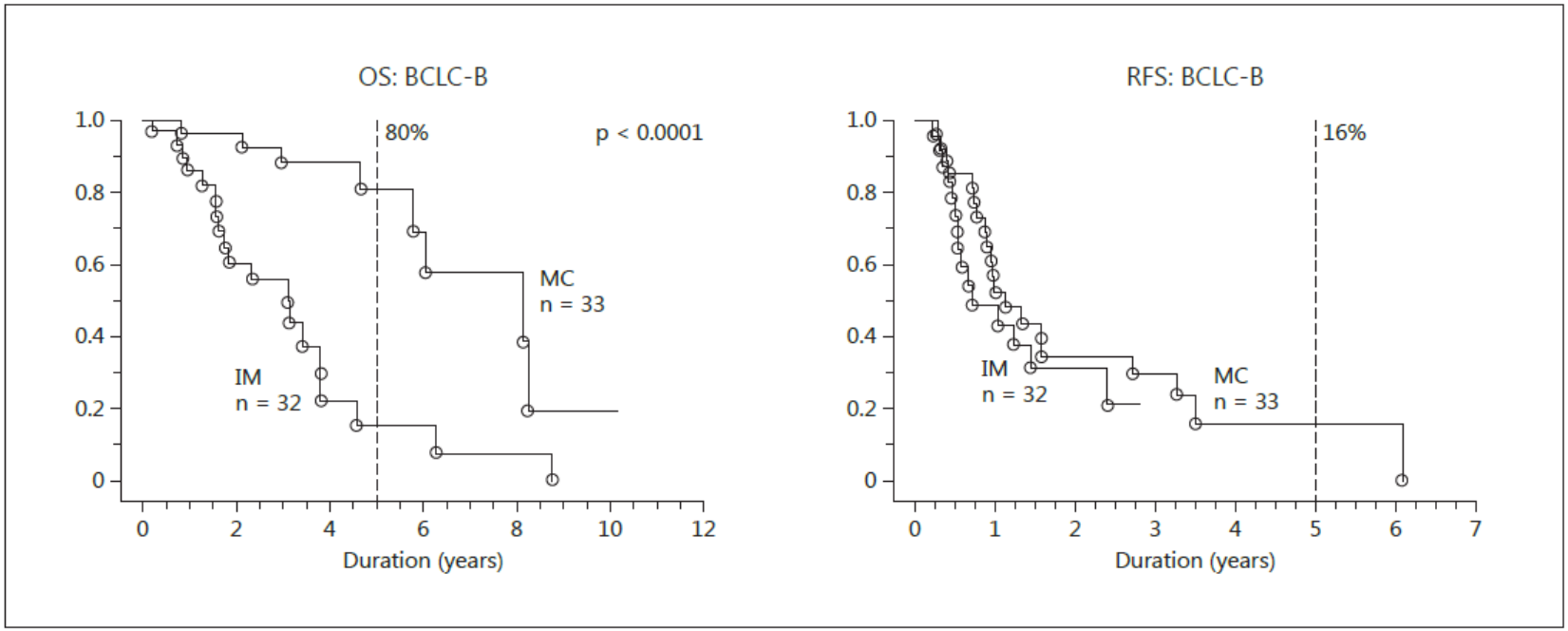
- Mostly based on histopathological findings:
  - Well differentiated foci of recurrent HCC are more likely to originate from a de novo process (i.e., MO-HCC)
  - Poor differentiation and invasive features point to metastatic dissemination (i.e., IM-HCC)

- Markers of tumor clonality may be necessary to accurately differentiate MO-HCC and IM-HCC

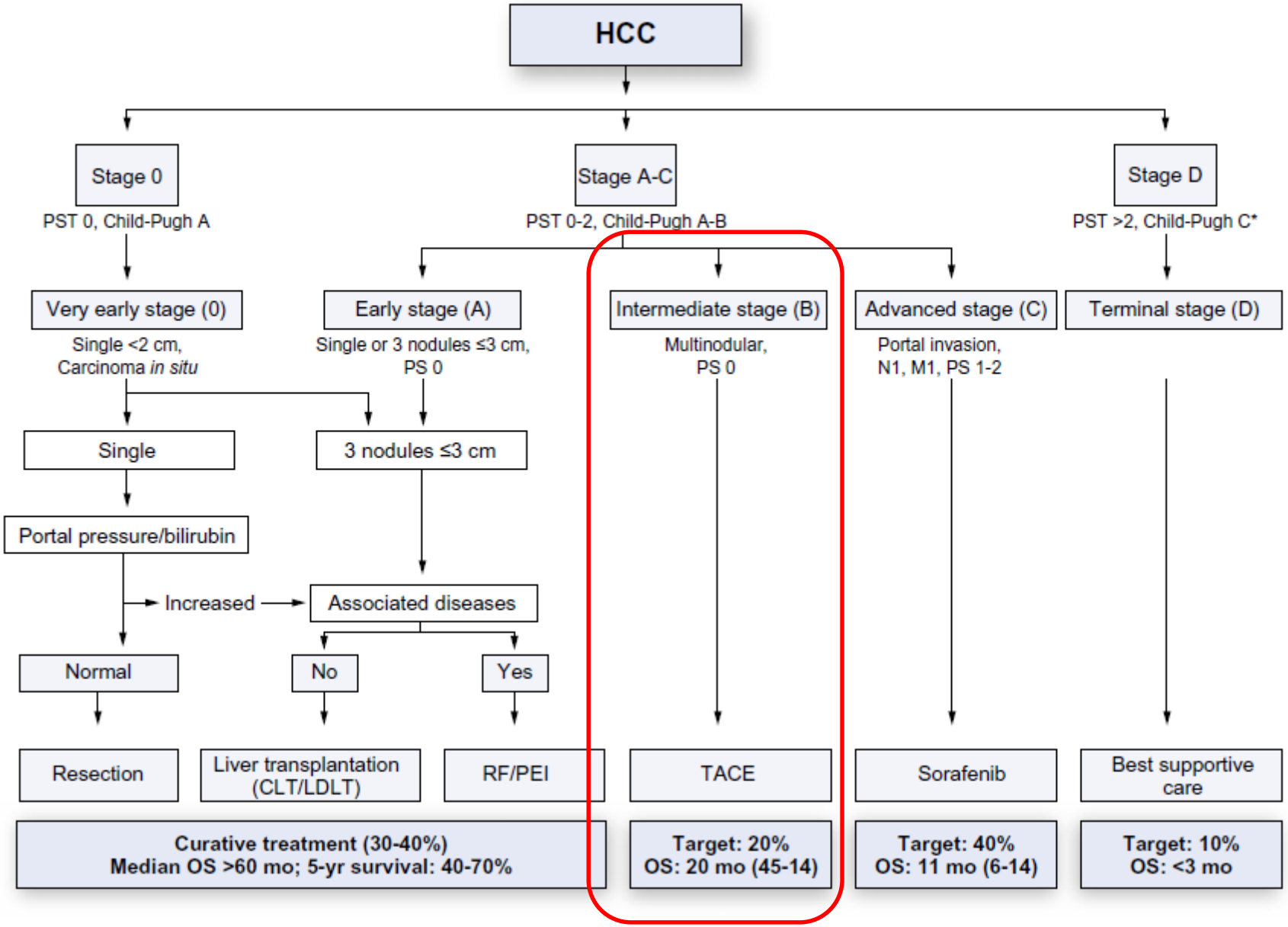
Radiofrequency ablation for intermediate-stage HCC – multi-centric vs. intra-hepatic metastasis

Overall Survival

Recurrence-Free Survival



Kariyama K, et Al. Oncology 2015



- Multi-centric HCC with small nodule is classified within intermediate BCLC stage; yet, each individual lesions may be an early HCC

Intermediate BCLC Stage B

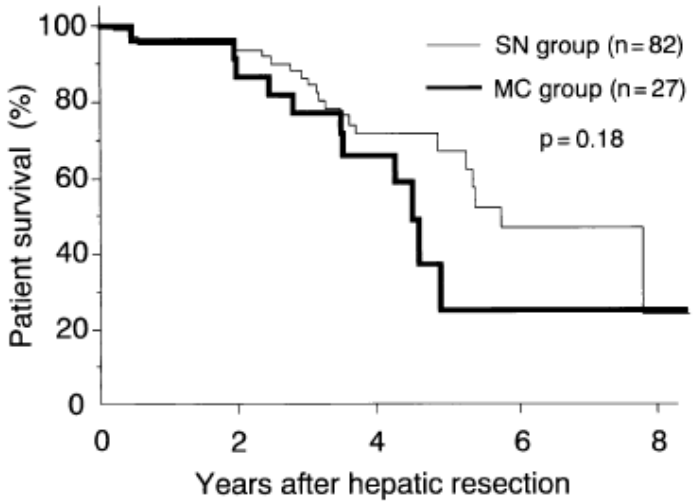
- BCLC stage B is a heterogeneous category with variable tumor burden and hepatic reserve
- Several studies proposed sub-classification system for intermediate stage HCC to better direct therapeutic interventions

Intermediate BCLC Stage B

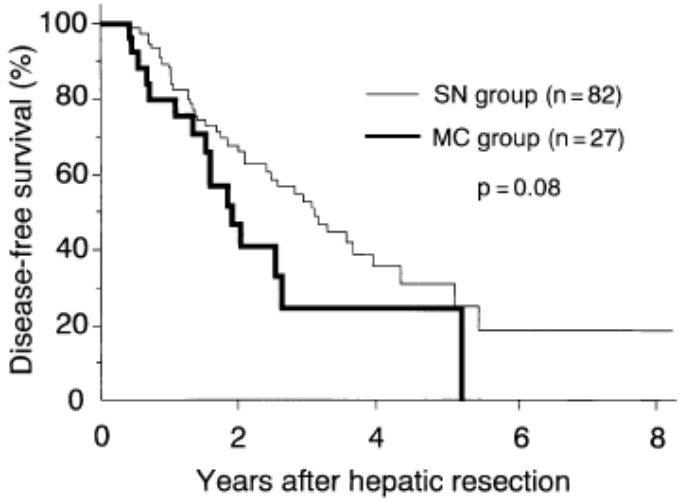
- Patients with HCC of BCLC stage B are primarily considered for TACE
- TACE extends survival of there patients up to 20 months (range 35-45 months)
- TARE is an emerging alternative/adjunct to TACE
- In some settings, resection will be offered because surgery has a curative potential

Hepatectomy for Multi-Centric Hepatocellular Carcinoma

Overall Survival



Disease-Free Survival



SN=Single Node; MC=Multi-Centric

- Patients with multi-centric HCC had worse hepatic functional reserve than patients with a single HCC

Utsunomiya T, et al. J Am Coll Surg 2000

Summary

- Discuss cases in multidisciplinary liver-oriented tumor-board
- Consult radiologists experienced in MRI (Including liver-specific contrast agents)
- “Map” the liver into segments with specific lesions
- Differentiate multiple HCC between MO-HCC and IM-HCC
- Perform a therapeutic plan including combinations of: resections/RFA/TACE/TARE in appropriate settings
- Consider transplantation in patients meeting criteria

Acknowledgment

- Dr. Lewis Roberts –
  Mayo Clinic, Rochester, Minnesota

- Dr. Michael Charlton –
  Intermountain Medical Center, Utah

- Prof. Marc Bourliere – Marseille, France