NEW OPTIONS TO TREAT ADVANCED HEPATOCELLULAR CARCINOMA

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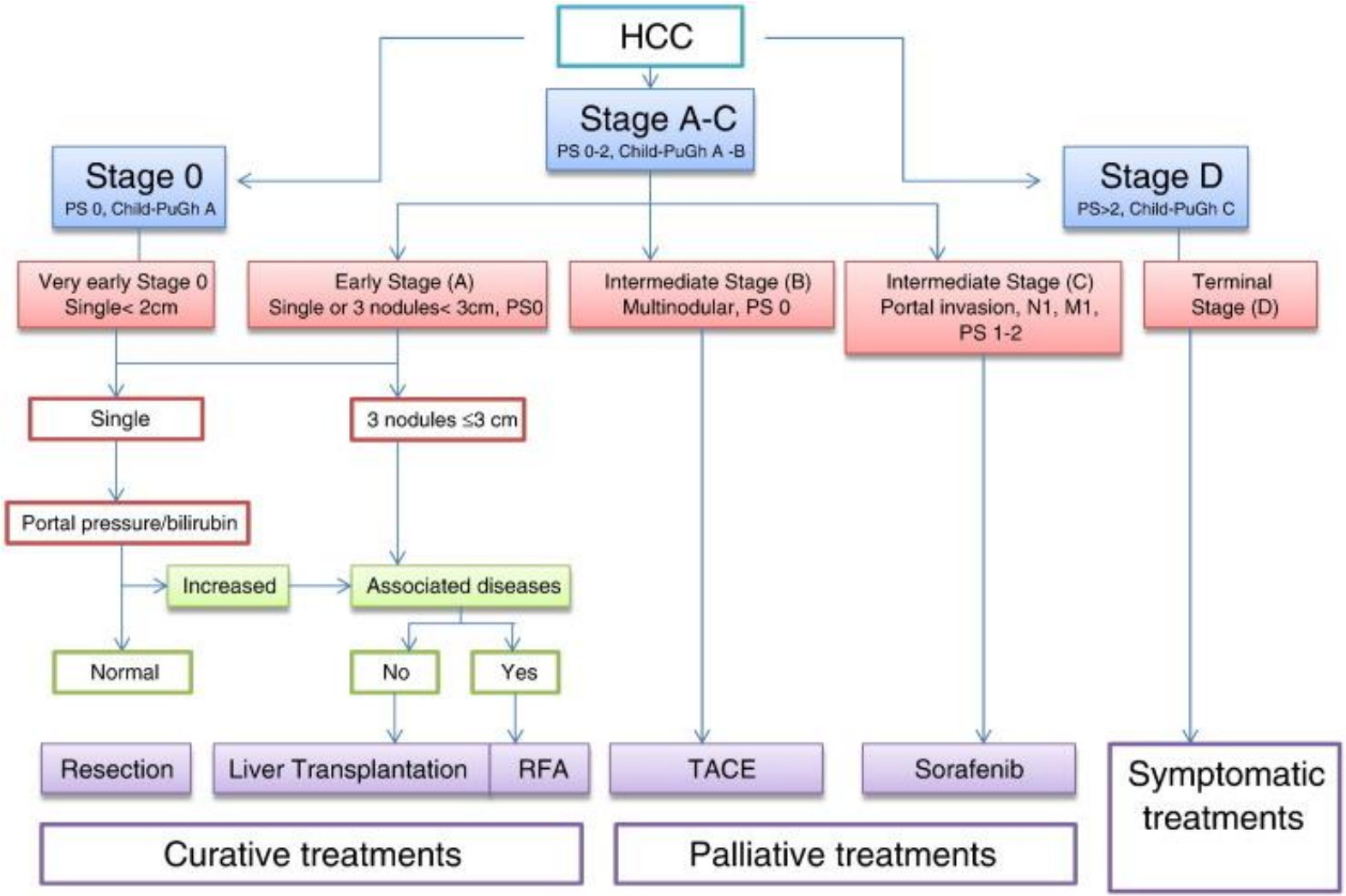
Learning Objectives

- Evaluate imaging criteria in HCC staging.
- Assess efficacy of biomarkers in early detection of HCC.
- Examine the effect of novel systemic agents on HCC.
- Identify the role of surgery and transplantation in treatment of HCC.

BCLC (Barcelona Clinic Liver Cancer) Staging



Bruix. Hepatology 2011;53(3): 1020-1022

CT/MRI LI-RADS® v2018 CORE

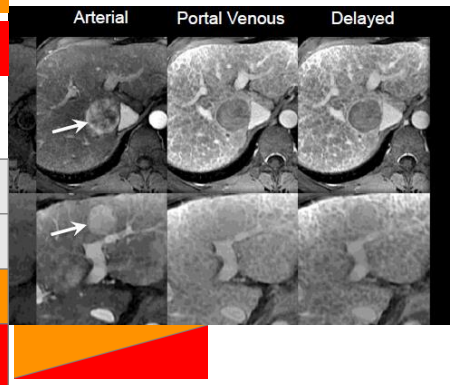
Liver Imaging Reporting And Data System

Untreated observation without pathologic proof in patient at high risk for HCC

- If cannot be categorized due to image degradation or omission → LR-NC
- If definite tumor in vein (TIV) → LR-TIV
- If definitely benign → LR-1
- If probably benign → LR-2
- If probably or definitely malignant but not HCC specific (e.g., if targetoid) → LR-M

Otherwise, use CT/MRI diagnostic table below

- If intermediate probability of malignancy → LR-3
- If probably HCC → LR-4
- If definitely HCC → LR-5



CT/MRI Diagnostic Table

Arterial phase hyperenhancement (APHE)		No APHE		Nonrim APHE		
Observation size (mm)		< 20	≥ 20	< 10	10-19	≥ 20
Count additional major features: • Enhancing "capsule" • Nonperipheral "washout" • Threshold growth	None	LR-3	LR-3	LR-3	LR-3	LR-4
	One	LR-3	LR-4	LR-4	LR-4 / LR-5	LR-5
	≥ Two	LR-4	LR-4	LR-4	LR-5	LR-5

LR-4 / LR-5

Observations in this cell are categorized based on one additional major feature:
- LR-4 – if enhancing "capsule"
- LR-5 – if nonperipheral "washout" **OR** threshold growth

If unsure about the presence of any major feature: characterize that feature as absent

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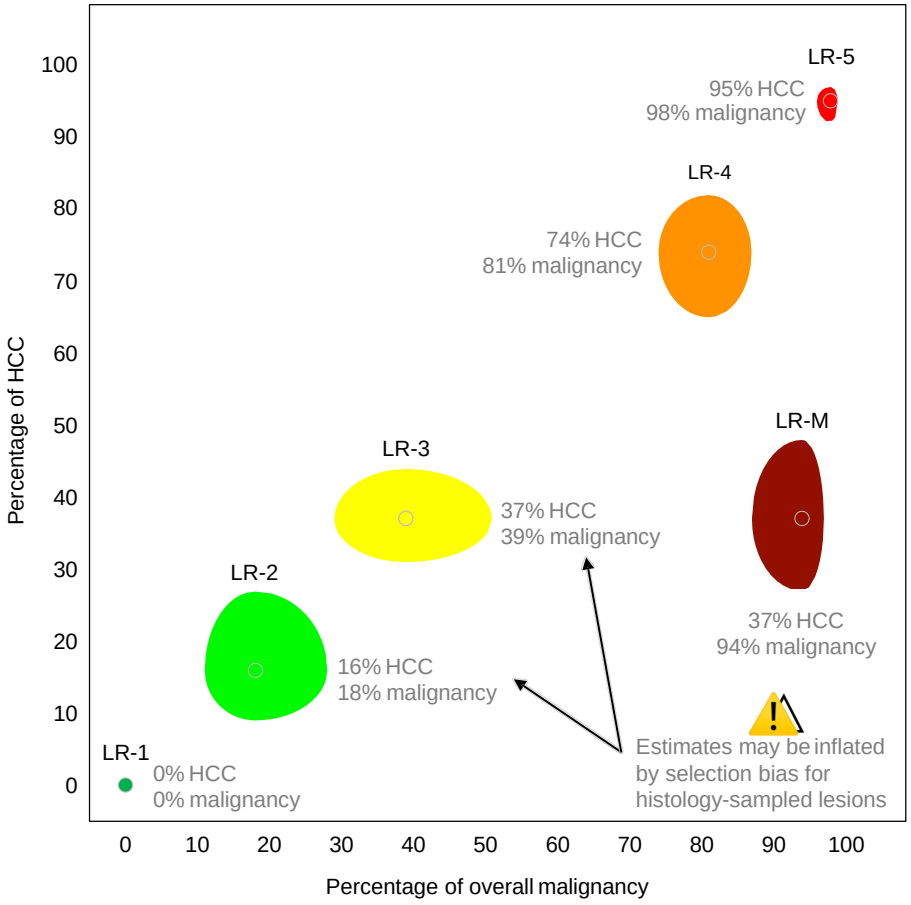
CT/MRI LI-RADS® v2018 CORE

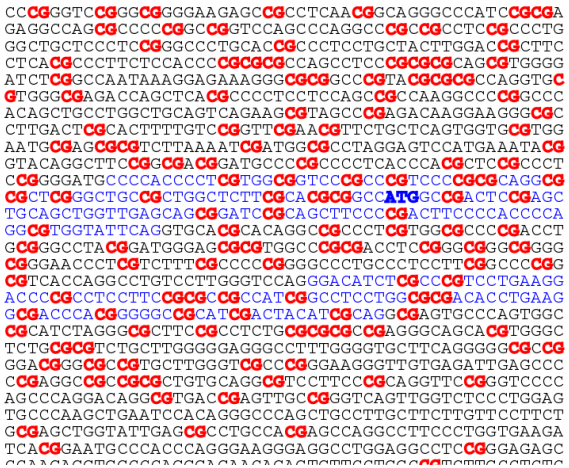
What is the percentage of HCC and malignancy associated with each LI-RADS category??

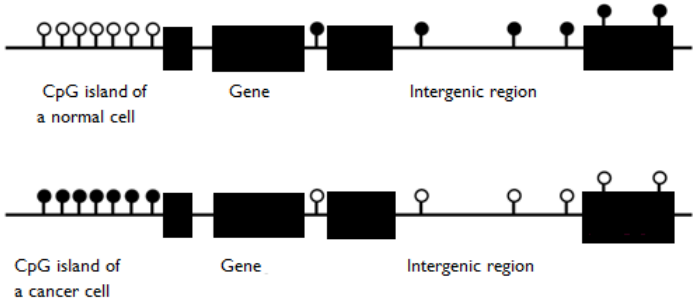
The percentage (with 95% confidence intervals) associated with LR-1, LR-2, LR-3, LR-4, LR-5, and LR-M is summarized below:



Methylated DNA

- Two of four bases can be methylated: cytosine, adenine
- In mammals, DNA methylation exclusively in CpG dinucleotides
  - 75% of CpG methylated in somatic cells- increases frequency of spontaneous mutations (CpG converts to TpG)
  - Exception: CpG islands that are unmethylated (>200 bp, GC content >50%)
  - 25,000 CpG islands in human genome, 50% in gene promoter regions
- In cancer: CpG islands acquire hypermethylation causing transcription silencing of DNA repair gene





Combined methylated DNA and protein markers: an accurate blood-based test for early-stage detection of hepatocellular carcinoma

Aim:

To identify a panel of blood-based biomarkers with high sensitivity for early-stage detection of hepatocellular carcinoma

Methods:

- Multi-center, case-control study
- Patient population: 135 HCC cases; 305 age- and liver disease etiology-matched controls
- Whole blood collected at clinical sites and shipped to central lab for processing; samples blinded upon delivery
- 10 methylated DNA markers (MDMs) and multiple proteins evaluated via logistic regression algorithm to classify samples as positive or negative for HCC

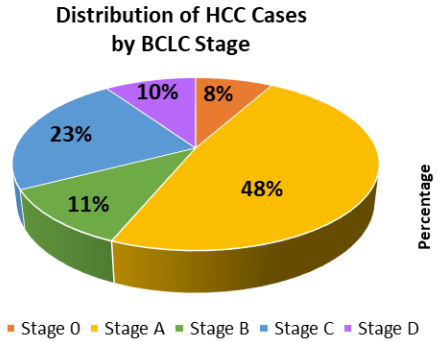
Main Findings:

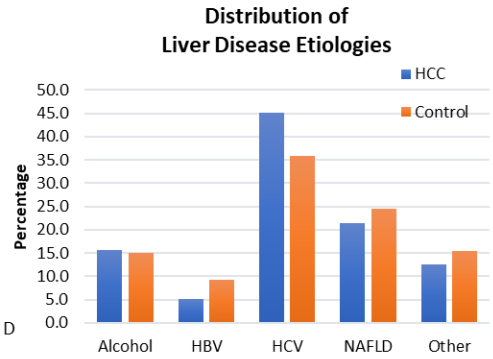
At 90% specificity, a panel of 4 MDMs (DAB2IP, EMX1, HOXA1, TSPYL5) and 2 proteins (AFP, AFP-L3) detected 71% of early-stage HCC.

Conclusions:

We identified a panel of 6 biomarkers with significantly higher sensitivity for early-stage HCC compared to AFP with or without AFP-L3.

Chalasani N, et al., Abstract 109





Biomarker Panel	Early Stage* Sensitivity (95% CI)	All Stage Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)
Exact (4 MDM + 2 Protein)	**71% (60-81%)**	**80% (72-86%)**	**90% (86-93%)**	**0.912 (89-94%)**
AFP (20 ng/mL)	21% (13-32%)	43% (35-52%)	98% (95-99%)	0.706 (66-76%)
AFP (100 ng/mL)	6.6% (2-15%)	27% (20-36%)	100% (99–100%)	0.637 (58-69%)
AFP (5 ng/mL) + AFP-L3 (4%)	37% (26-49%)	55% (46-63%)	94% (90–96%)	0.795 (75-84%)

*Early Stage = BCLC Stage 0 and A

Direct-acting antiviral therapy for HCV infection is associated with increased survival in patients with a history of hepatocellular carcinoma

Aim:

Evaluate if direct acting antiviral (DAA) therapy improves survival in patients with a history of complete response to hepatocellular carcinoma (HCC) treatment

Methods:

Multicenter retrospective cohort study examining the association between DAA therapy and all-cause mortality in 797 patients with hepatitis C-related HCC who achieved complete response to HCC treatment

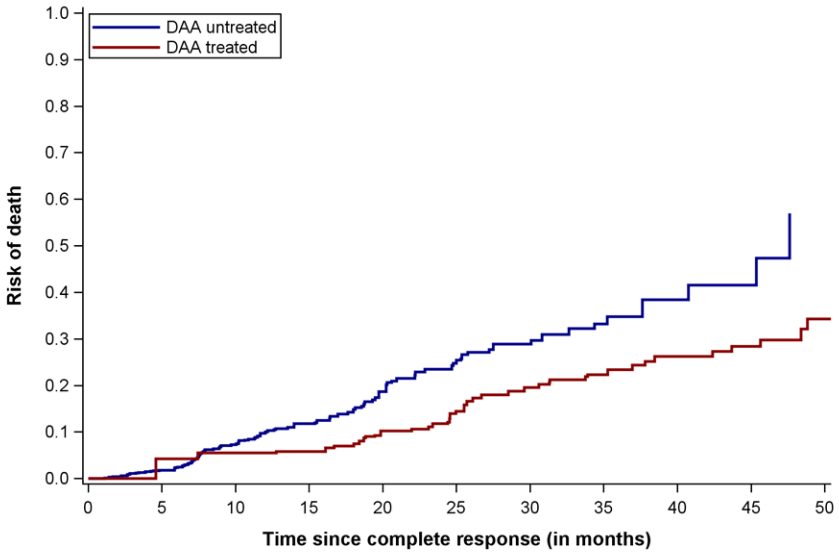
Main Findings:

DAA therapy was associated with significantly reduced mortality (HR 0.54, 95% CI 0.33–0.90); this association was observed in patients who achieved SVR (HR 0.29, 95% CI 0.18–0.47) but not those without SVR (HR 1.13, 95% CI 0.55–2.33).

Conclusions:

In a large cohort of North American patients with complete response to HCC treatment, DAA therapy was associated with significantly reduced mortality.

Singal AG, et al., Abstract 199



797 patients with HCV-related HCC:

- 383 (48.1%) received DAA therapy
- 414 (51.9%) were untreated

Deaths:

- 43 deaths occurred during 941 person-years of follow-up among DAA
- 103 deaths during 527 person-years among DAA-untreated patients
- crude rate ratio 0.23, 95% CI 0.16–0.33

- Median time from HCC complete response to death:
  - 25.7 (IQR 19.4–33.9) months- DAA-treated patients
  - 11.5 (IQR 7.1–20.2) months- untreated patients

Multivariable analyses:

- DAA therapy was associated with significantly reduced mortality (HR 0.39, 95% CI 0.26–0.61)
- Association driven by SVR, with reduced mortality observed in DAA-treated patients who achieved SVR (HR 0.26, 95% CI 0.16–0.42) but not those without SVR (HR 0.78, 95% CI 0.40-1.52).
- Greater benefit of DAA therapy in patients who remained HCC recurrence-free (HR 0.09, 95% CI 0.02–0.34) compared to those who experienced recurrence (HR 0.62, 95% CI 0.37–1.04) (interaction p-value=0.01).

LXR agonism potentiates sorafenib activity in HCC by inducing metabolic stress

Objective:

To identify druggable targets to enhance sorafenib efficiency

Methods:

- Use of novel *in vivo* cDNA screen to identify genes required for tumor progression with and without sorafenib
- *In vitro* confirmatory assays including drug screens, RNA sequencing, siRNA

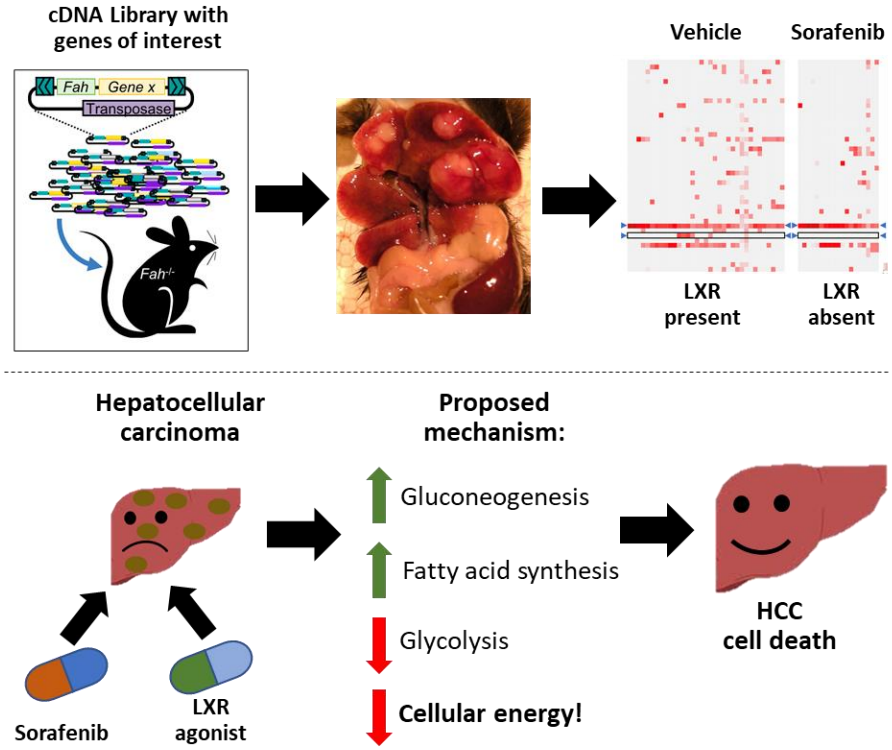
Main Findings:

- Sorafenib-resistant tumors do not develop in the presence of LXR.
- LXR agonism and sorafenib combination targets HCC more effectively *in vitro* compared to sorafenib monotherapy.
- Combination therapy alters expression of metabolic genes, and silencing PCK2 (gluconeogenesis) and FASN (fatty acid synthesis) protect against cell death.

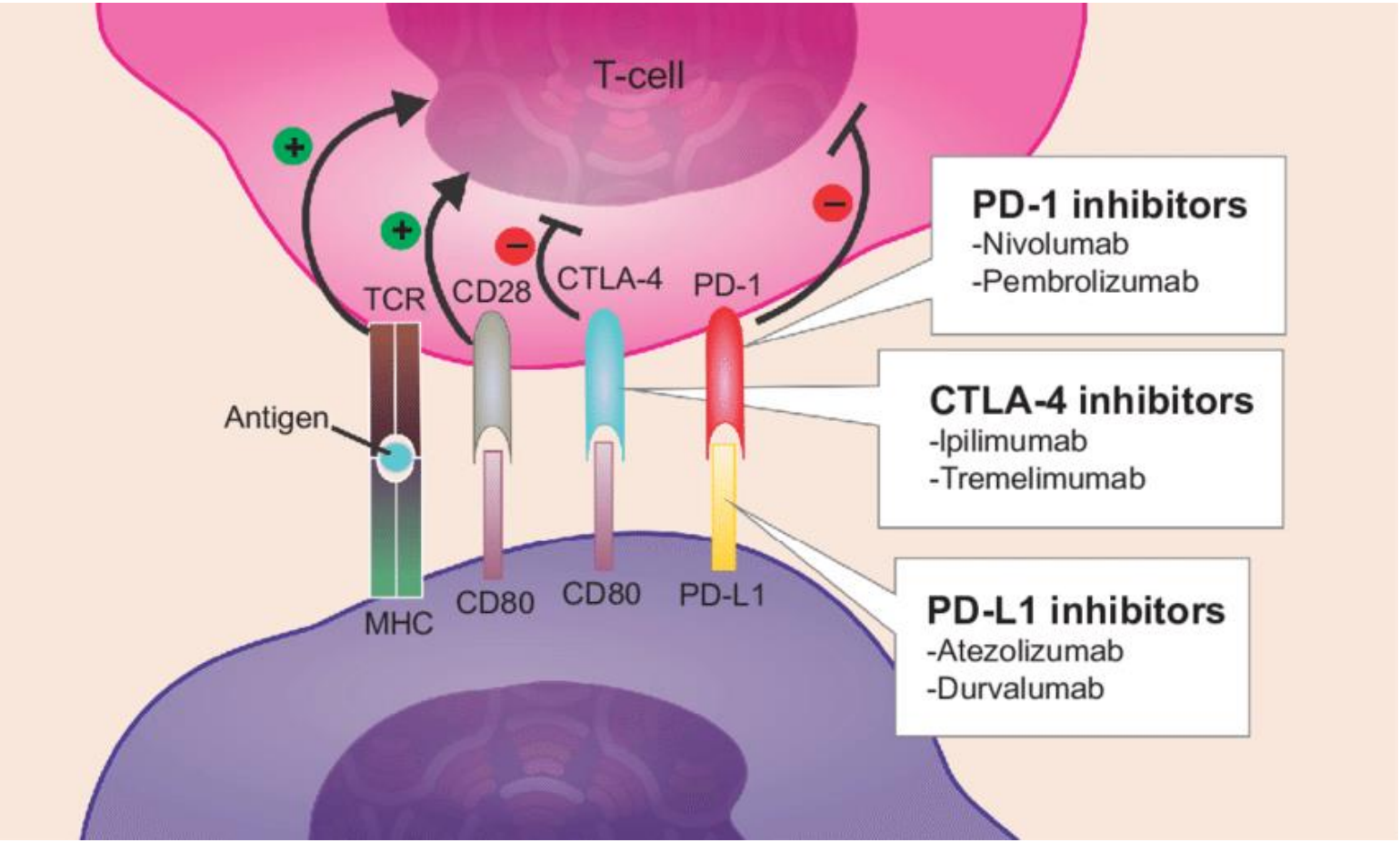
Conclusions:

Our novel *in vivo* genetic screen led to identification of LXR agonism as an effective dual therapy with sorafenib *in vitro*. Combination therapy effectively targets HCC through metabolic changes, likely involving increased gluconeogenesis and fatty acid synthesis, and decreased glycolysis.

Preziosi ME, et al., Abstract 112



Immune Checkpoint Inhibitors



CheckMate 040: nivolumab + ipilimumab in patients with advanced hepatocellular carcinoma (aHCC)

Objective:

To assess the safety and efficacy of nivolumab (NIVO; PD-1 inhibitor) plus ipilimumab (IPI; CTLA-4 inhibitor) in the CheckMate-040 study, the first prospective study of this immunotherapy combination in patients with aHCC treated with sorafenib

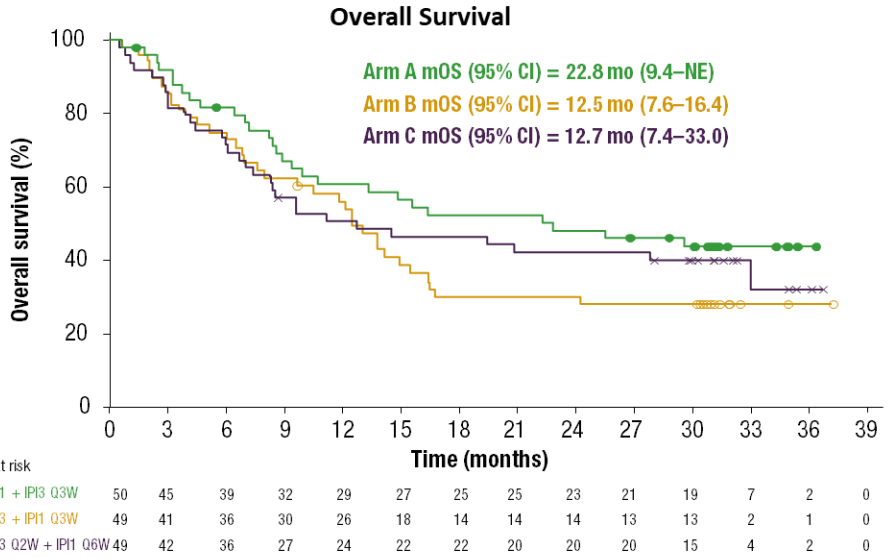
Methods:

Patients treated with SOR were randomized to 3 arms: [A] NIVO 1 mg/kg + IPI 3 mg/kg Q3W (4 doses) or [B] NIVO 3 mg/kg + IPI 1 mg/kg Q3W (4 doses), each followed by NIVO 240 mg Q2W, or [C] NIVO 3 mg/kg Q2W + IPI 1 mg/kg Q6W, until intolerable toxicity or disease progression. Primary endpoints were safety and tolerability, objective response rate (ORR), and duration of response (DOR; investigator assessment using RECIST v1.1).

Main Findings:

- Investigator-assessed ORR: 32%, 27%, and 29% in arms A, B, and C, respectively, concordant with BICR-assessed responses; median DOR: 17.5, 22.2, and 16.6 months, respectively.
- Any-grade immune-mediated hepatic AEs: 20%, 12%, and 6% of patients in arms A, B, and C, respectively
  - The proportion of hepatic events (median time to resolution) that resolved: 90% (6.6 weeks) in arm A, 83% (7.9 weeks) in arm B, and 67% (6.1 weeks) in arm C.
  - Of the 10, 6, and 3 patients who had an immune-mediated hepatic AE, 7, 3, and 2 patients received high-dose glucocorticoids (≥ 40 mg of prednisone per day or equivalent) for a median (range) of 2 weeks (0.4–147.6), 1 week (0.6 –1.1), and 3 weeks (2.0–3.0) in arms A, B, and C, respectively.
  - No patients who were rechallenged with NIVO or IPI after experiencing an immune-mediated hepatic AE experienced a recurrence of the event.

Sangro B, et al, Abstract 200



AE, adverse event; BICR, blinded independent central review; CI, confidence interval; CTLA-4, cytotoxic T-lymphocyte antigen; mOS, median overall survival; NE, not estimable; PD-1, programmed death-1; Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

Conclusions:

NIVO + IPI demonstrated durable responses and a manageable safety profile in patients with aHCC treated with SOR.

Laparoscopic versus open hepatectomy for large HCC: a randomized controlled study

Aim:

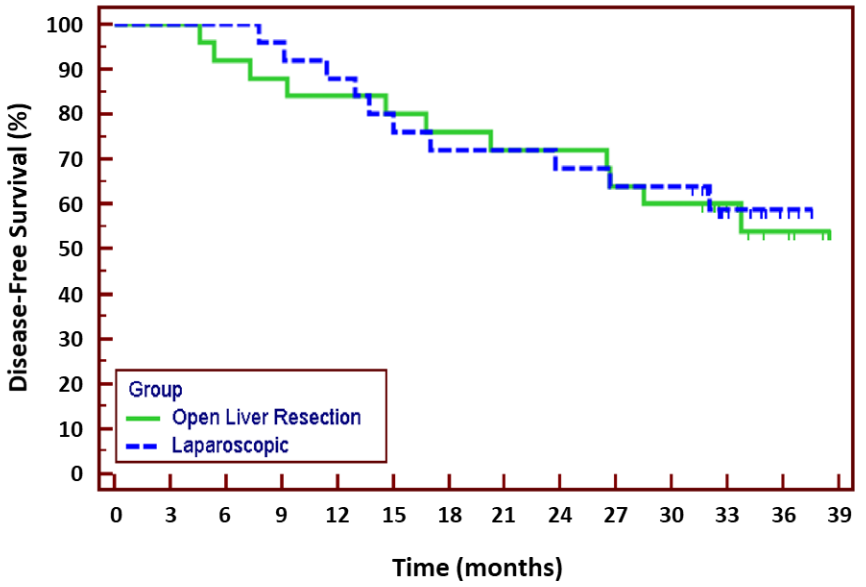
- Strong evidence from prospective studies for the superiority of either the open or laparoscopic approach is still lacking.
- Aim was to compare feasibility, safety, surgical and oncologic efficiency of laparoscopic versus open hepatetcomy (OH) in management of solitary large (>5 cm).

Methods:

150 Child A cirrhotic patients with large HCC met the inclusion criteria and were randomly assigned to either OH group (75 patients) or LH group (75 patients).

Conclusions:

LH is superior to the OH with significantly shorter duration of hospital stay with no compromise to oncological outcomes and similar disease-free survival compared to OH.



Elgendi AM, et al., Abstract 223

Surgical treatment is associated with improved outcome in patients with single less than 2 cm hepatocellular carcinoma

Aim:

To investigate the impact of treatment on outcomes of single <2 cm HCCs

Methods:

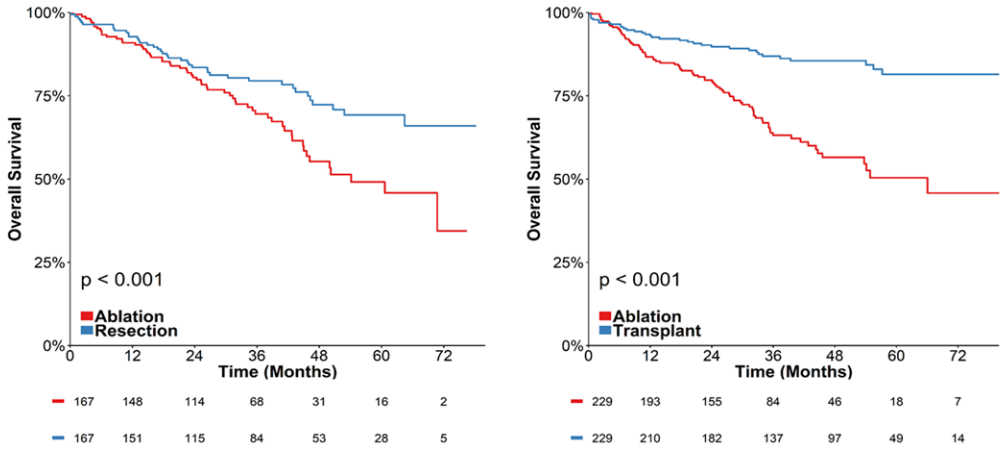
HCC diagnosed between 2004 and 2014 from the NCDB

Main Findings:

Liver transplant (HR: 0.27; 95% CI: 0.20-0.37; *P*<0.01) or resection (HR: 0.67; 95% CI: 0.48-0.93; *P*=0.02) was independently associated with an improved survival compared to ablation. The superiority of surgical treatment remained after propensity score matchings and inversed probability weighting adjusted analysis.

Conclusions:

Surgical treatment was associated with longer survival in patients with single <2 cm HCC.



Yang JD, et al., Abstract 224

Six-month waiting rule was associated with lower waitlist mortality/drop-out in LT candidates with HCC

Aim:

To evaluate effects of the 6-month waiting rule on waitlist outcomes in patients with hepatocellular carcinoma (HCC)

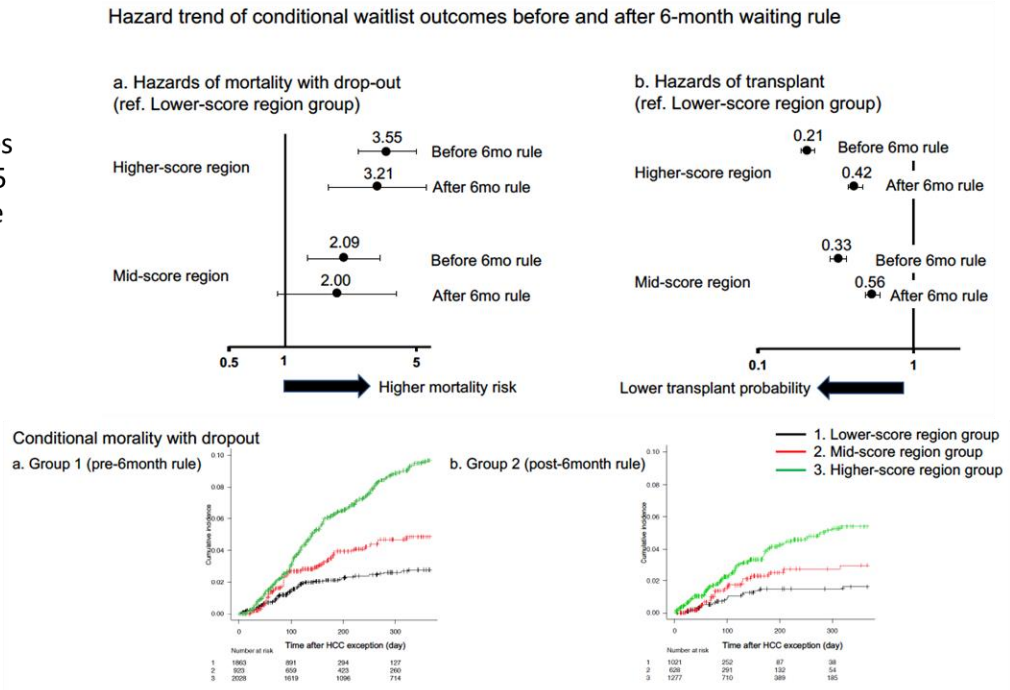
Methods:

- Group 1 (pre 6-month rule) comprises transplant candidates with HCC exception scores from Jan. 1, 2013 to Oct. 7, 2015 (n=4814) and Group 2 (post 6-month rule) comprised those from Oct. 8, 2015 to Jun. 30, 2018 (n=3287).
- Conditional waitlist outcomes, defined as outcomes from the time of HCC exception scores were given, were compared between UNOS region groups according to transplant MELD scores (lower: region 3, 10, and 11, mid: 1, 2, 6, 8, and 9, higher: 4, 5, and 7).

Conclusions:

The mandatory 6-month waiting time rule in the HCC exception policy decreased waitlist mortality/dropout and increased transplant probability with increasing regional parity of liver transplant.

Nagai S, Moonka D, et al., Abstract 225



A US multicenter analysis of 2529 HCC patients undergoing liver transplantation: 10-year outcome assessing the role of downstaging to within Milan criteria

Aim:

Evaluate the 10-year outcomes of downstaging to within Milan Criteria (MC) prior to liver transplantation (LT)

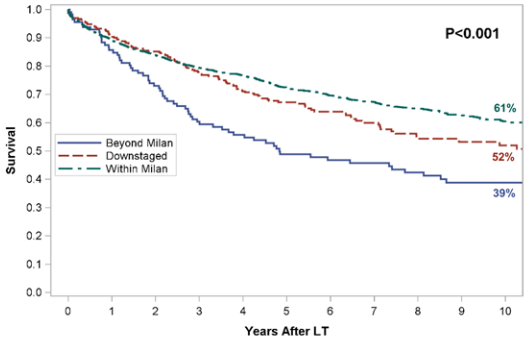
Methods:

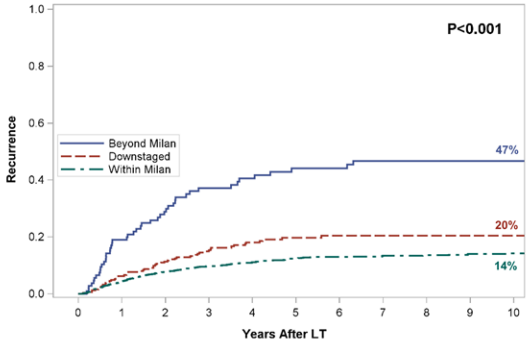
- A total of 2529 adult patients undergoing LT for HCC from 2001-2015 from 5 large US centers were reviewed.
- Outcomes of patients downstaged (n=330) to within MC (radiographic) were compared to patients within MC (n=2086) and those transplanted beyond MC (n = 110).
- Predictors of downstaging failure and recurrence-free survival were identified.

Conclusions:

- We report excellent 10-year post-LT outcomes in patients with HCC successfully downstaged to within MC, thus validating national downstaging policy.
- Tumor characteristics (> 3 nodules; diameter >7 cm) and lack of AFP response prior to LT were factors independently associated with downstaging failure.

Tabrizian P, et al., Abstract 15





Predictors of downstaging failure	OR (95% CI)	*P*-Value
Tumor numbers at diagnosis > 3	OR 2.30 (1.17 - 4.51)	0.015
Maximal initial tumor diameter > 7 cm	OR 2.70 (1.30 - 5.77)	0.011
Lack of AFP response to LRT	OR 2.49 (1.24 - 4.49)	0.009
Predictors of poor recurrence-free survival (downstaged cohort)	**HR (95% CI)**	***P*-Value**
Maximum viable tumor diameter > 5 cm	HR 2.49 (1.51 - 4.09)	< 0.001
Pre-LT NLR > 5	HR 2.20 (1.39 - 3.47)	< 0.001
Pre-LT AFP > 20 ng/mL	HR 1.59 (1.09 - 2.31)	0.015

Impact of Healthy Lifestyle on incidence of HCC & Cirrhosis related Mortality among US adults (Simon TG et al)

- Prospective cohort study of adults without known liver disease at baseline
- 121,893 adults followed for 2,388,811 person-years
- 121 incident HCC and 350 cirrhosis-related deaths
- Five modifiable risk factors: smoking, alcohol use, BMI, physical activity, healthy diet
- HR for 5 versus 0 risk factors: 3.59 for incident HCC and 4.27 for cirrhosis related mortality
- Overall, single factor with largest population-attributable risk was overweight/obesity (BMI ≥25)


"Thats all Folks!"