2019 LIVER SYMPOSIUM

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AASLD 2019: HCC Update

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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)

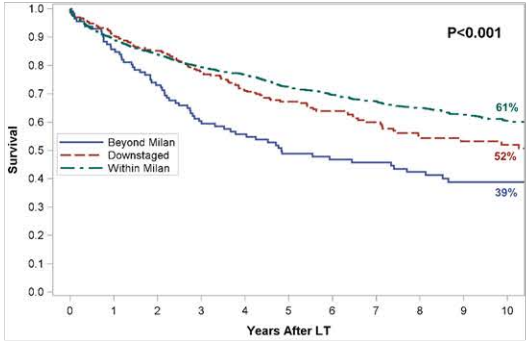
Methods:

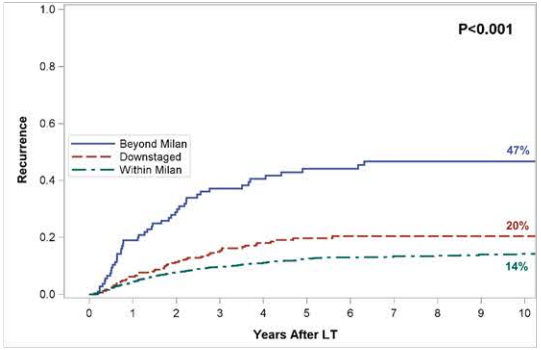
- A total of 2529 adult patients undergoing LT for HCC from 2001-2015 from 5 large US centers were reviewed.
- Outcomes of patients downstaged (n=330) to within MC (radiographic) were compared to patients within MC (n=2086) and those transplanted beyond MC (n=110).
- Predictors of downstaging failure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

Chromosomal rearrangements of *ROS1*, *FRK*, and *IL6* in inflammatory hepatocellular adenomas

Hypothesis and Aim:

- Inflammatory hepatocellular adenomas are benign liver tumors characterized by an activation of the JAK/STAT pathway caused by oncogenic activating mutations.
- However, a subset of these tumors lacks identified mutation explaining the inflammatory phenotype.

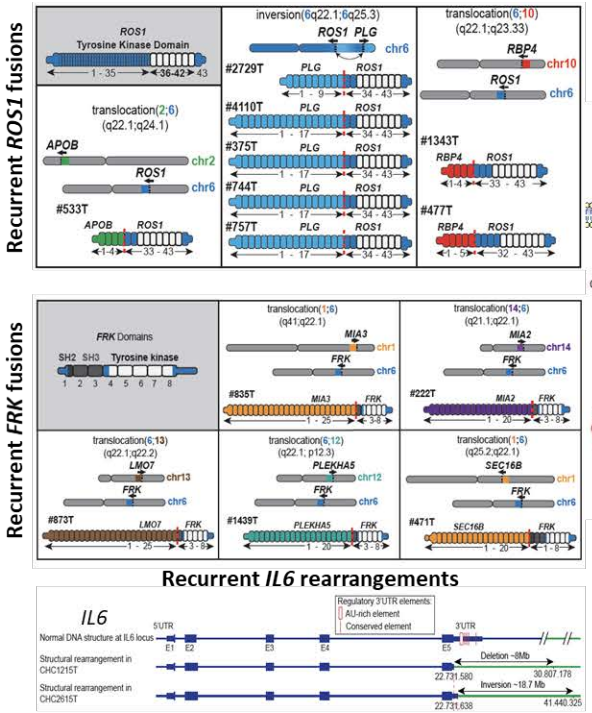
Methods:

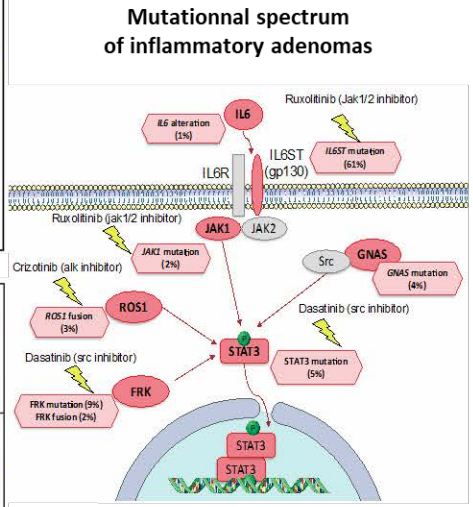
Analysis of 657 HCA developed in 504 patients for gene expression of 17 genes and for mutations in 7 genes by sequencing. 22 non-mutated IHCAs were analyzed by whole-exome and/or RNA sequencing.

Conclusions:

Recurrent chromosomal alterations involving druggable *ROS1*, *FRK,* or *IL6* genes lead to constitutive activation of the JAK/STAT pathway in inflammatory hepatocellular adenomas.

Nault JC, et al., Abstract 28





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:

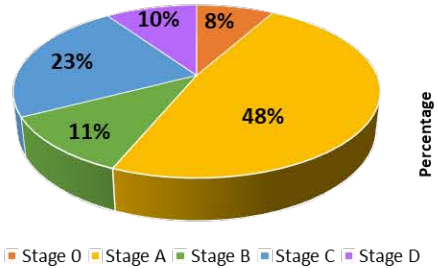
At 90% specificity, a panel of 4 MDMs (DAB2IP, EMX1, HOXA1, TSPYL5) and 2 proteins (AFP, AFP-L3) detected 71% of early-stage HCC.

Conclusions:

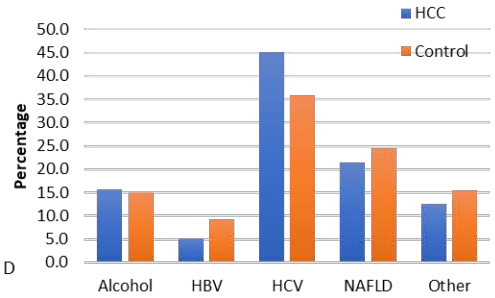
We identified a panel of 6 biomarkers with significantly higher sensitivity for early-stage HCC compared to AFP with or without AFP-L3.

Chalasani N, et al., Abstract 109

Distribution of HCC Cases by BCLC Stage



Distribution of Liver Disease Etiologies



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

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

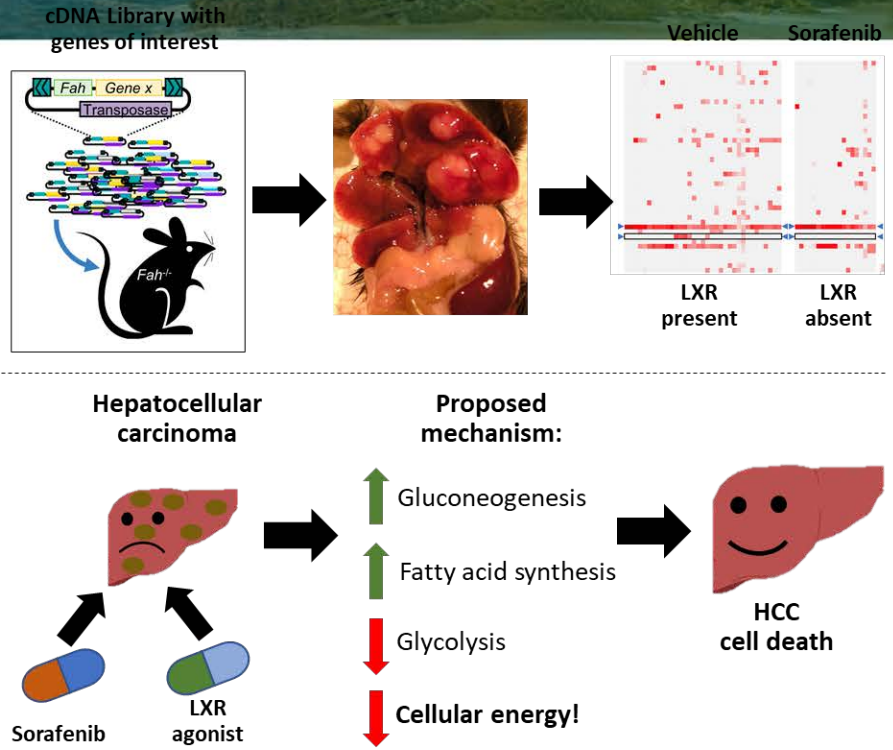
Main Findings:

- 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 changes during the early steps of human liver carcinogenesis

Aim:

The immune modulations involved in the early steps of human liver carcinogenesis remain unknown. We aimed to characterize the in situ immune changes occurring in dysplastic/transformed cirrhotic macronodules (MN).

Methods:

A series of 127 MN of all stages was investigated. The densities of the immune cells were assessed by image analysis software. Gene expression profiling was performed in a subset of lesions.

Main Findings:

Compared to adjacent cirrhotic nodules, increased densities of T cells, B cells, and dendritic cells were observed in MN. Tertiary lymphoid structures were identified in 24% of MN. We identified a subset of MN with up-regulation of genes involved in immune cell recruitment, antigen presentation, and T and B cell function. These lesions also showed overexpression of immune checkpoint inhibitory molecules.

Conclusions:

Our study shows that in situ immune responses occur in a subset of MN, and the expression of immune checkpoint molecules and pro-carcinogenic cytokines in this subgroup of lesions may favor immune evasion and allow the progression to full-blown HCC.

Meylan M, et al., Abstract 169

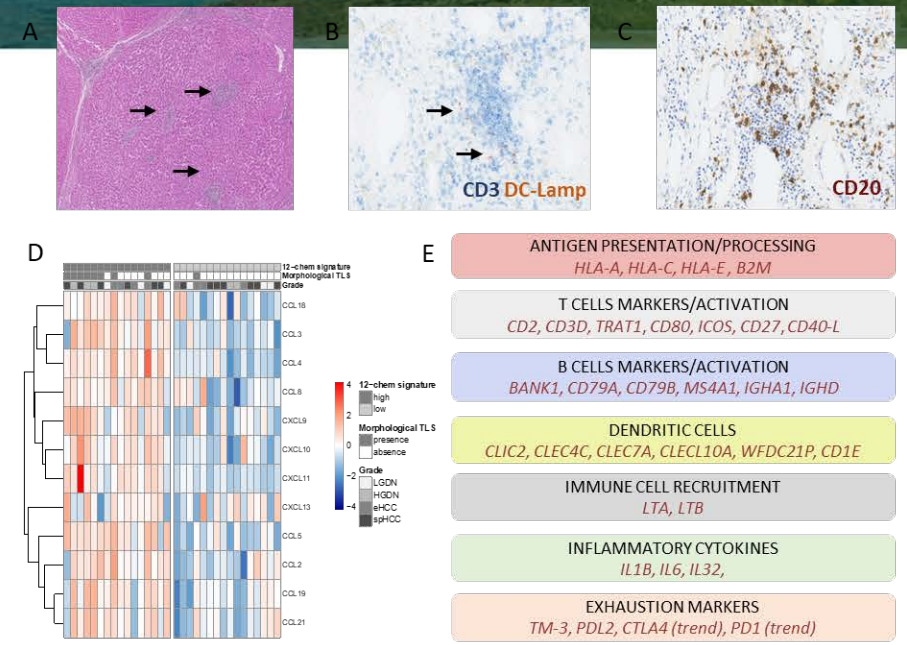


Figure. A subset of macronodules (MN) display tertiary lymphoid structures (TLS) and immune activation.
A) A case of MN with TLS (black arrows, X30). B and C) Immunohsitochemistry of a TLS with numerous DC-Lamp + dendritic cells (black arrows, red staining) in the vicinity of a T cell aggregate (CD3 : blue, X230). The TLS also includes CD20+ B cells. D) Gene expression profiling identifies a subset a MN with upregulation of a gene signature that includes 12 chemokines related to TLS induction and formation. E) MN with activation of the gene signature also shows upregulation of various genes involved in immune response.

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:

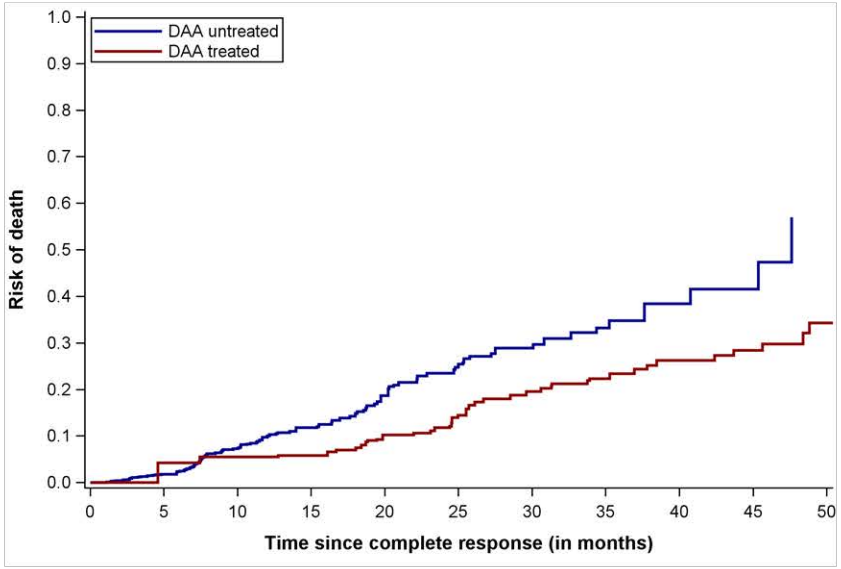
Multicenter retrospective cohort study examining the association between DAA therapy and all-cause mortality in 797 patients with hepatitis C-related HCC who achieved complete response to HCC treatment

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

HCV cure by all-oral DAA improves 5-year overall and liver-related survival in HCV-related HCC patients: a real-world, propensity score-matched study from both east and west

Objective:

To compare survival rates between HCV-related HCC patients who were untreated for HCV and those who achieved SVR with DAA treatment

Methods:

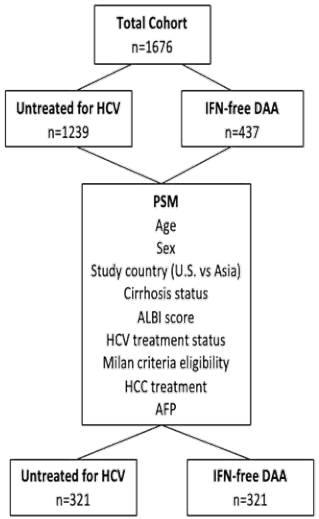
- 8 study sites: Two U.S. medical centers and six Asia medical centers (Korea, Japan, and Taiwan)
- 1:1 propensity score-matching; HCV treatment status as a time-varying covariate for Kaplan-Meier analysis and multivariable cox regression; landmark analysis

Conclusions:

HCV-related HCC patients with SVR achieved a 60-70% improvement in 5-year survival (both all-cause and liver-related) compared to patients untreated for HCV.

Dang H, et al., Abstract 40

Study flow chart

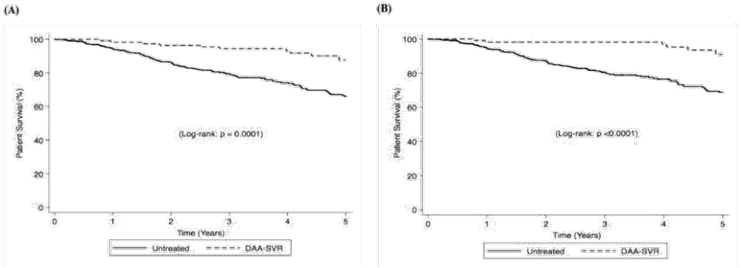


Predictors of mortality in PSM HCV-related HCC patients

Type of mortality	HCV treatment status	Adjusted HR* (95% CI)	P-value
All-cause	Untreated for HCV	Referent	Referent
	SVR	0.37 (0.16 – 0.83)	**0.016**
Liver-related	Untreated for HCV	Referent	Referent
	SVR	0.34 (0.13 – 0.88)	**0.026**

*Adjusted for age, sex, race/ethnicity, study country/region, diabetes, cirrhosis, MELD scores, HCC diagnosis year, AFP, BCLC stage, and HCC treatment type

Five-year Survival in PSM Patients Who Were Untreated for HCV or Had SVR After IFN-free DAA Treatment, with Time-Varying Adjustment for HCV Treatment Start Time. (A) All-cause Mortality. (B) Liver-related Mortality



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

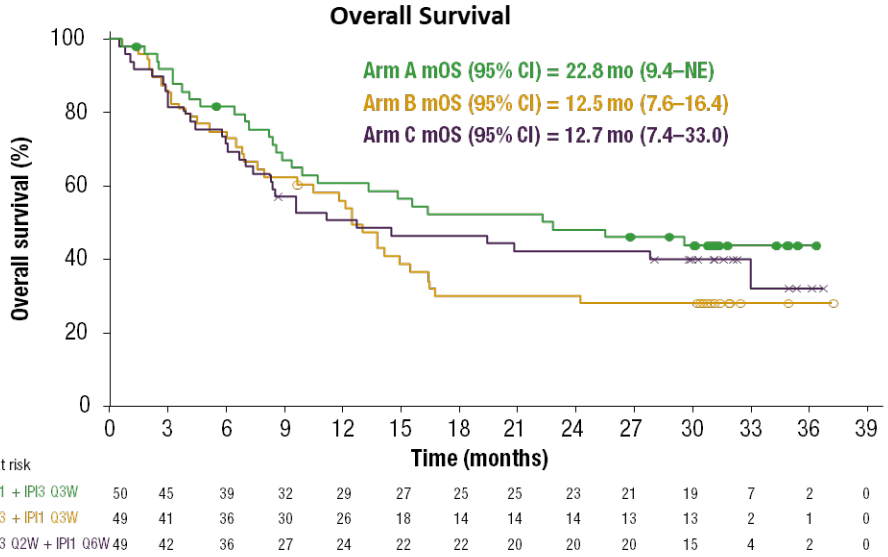
Methods:

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.

Financial burden is common in patients with cirrhosis and associated with lower HCC surveillance receipt

Aim:

Characterize the association between patient attitudes and barriers and HCC surveillance receipt in a large cohort of patients with cirrhosis

Methods:

Telephone-based survey study among 1021 patients with cirrhosis followed at 3 health systems (tertiary care referral center, safety-net health system, and VA hospital) in the United States

Main Findings:

Financial distress from medical care is common in patients with cirrhosis (10% delay care, 25% are unable to cover co-pays, 43% worry about medical bills) and is associated with significantly lower odds of HCC surveillance receipt (Table).

Conclusions:

Financial burden of medical care represents a potential intervention target to improve HCC surveillance effectiveness in the US.

Table. Correlates of HCC Surveillance in Year Prior to Survey

Variables	Odds Ratio (95% CI)
Age < 50 (vs 61-90) years	1.56 (95% CI 1.03 – 2.36)
Widowed (vs married) status	0.59 (95% CI 0.37 – 0.93)
Child Pugh B (vs Child Pugh A)	1.76 (95% CI 1.29 – 2.40)
Hepatology subspecialty care	5.60 (95% CI 4.01 – 7. 84)
Lack of health insurance	0.53 (95% CI 0.33 – 0.86)
Financial burden resulting in medical care delays	0.73 (95% CI 0.54 – 0.98)

Singal AG, et al., Abstract 201

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

Aim:

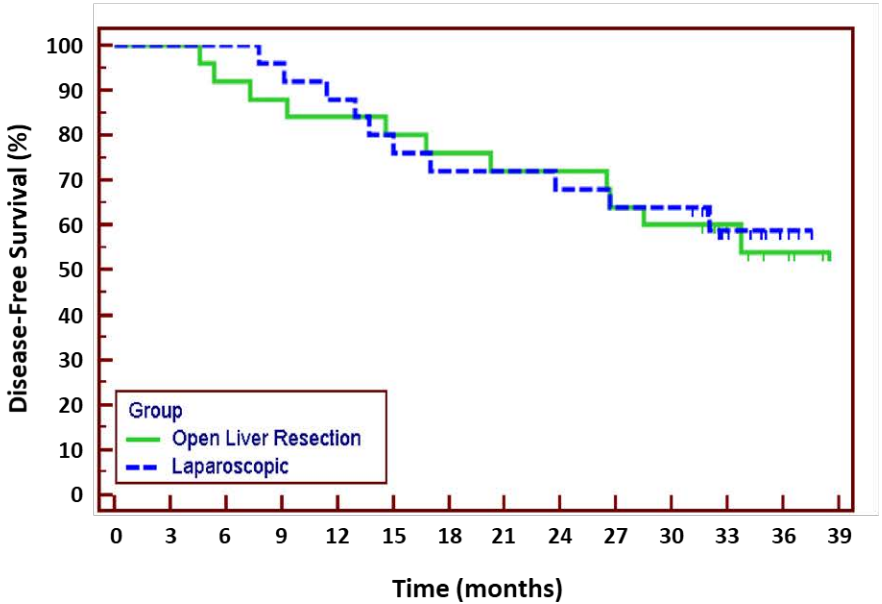
- Strong evidence from prospective studies for the superiority of either the open or laparoscopic approach is still lacking.
- Aim was to compare feasibility, safety, surgical and oncologic efficiency of laparoscopic versus open hepatetcomy (OH) in management of solitary large (>5 cm).

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:

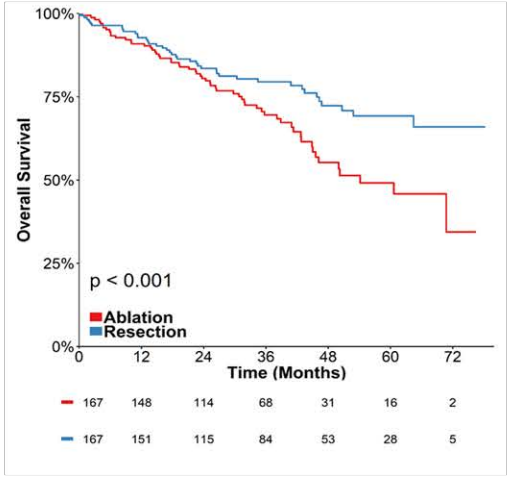
HCC diagnosed between 2004 and 2014 from the NCDB

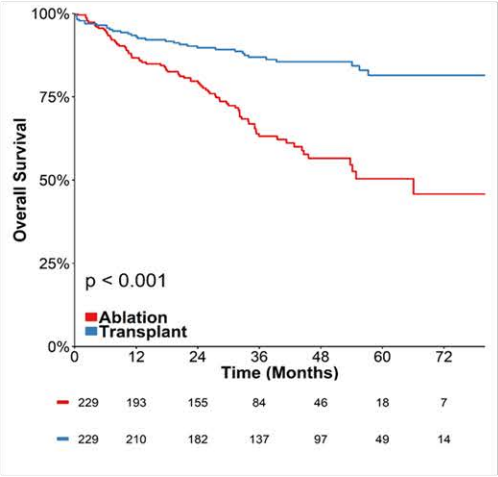
Main Findings:

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