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Northern California Society for Clinical Gastroenterology

Current and Developing Strategies in the Management of HCC

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I have no financial relationships to disclose within the past 12 months relevant to my presentation

AND

My presentation does not include discussion of off-label or investigational use

Overview

- Diagnostic criteria for HCC (update)
- Surveillance
- HCC and HBV
- Liver transplant for HCC

Overview

- Diagnostic criteria for HCC (update)
- Surveillance
- HCC and HBV
- Liver transplant for HCC

No major breakthrough in HCC treatment

DIAGNOSTIC CRITERIA FOR HCC
AASLD GUIDELINES (MODIFIED)

Tumor > 1 cm - One imaging (multi-phase CT/MRI) showing typical HCC characteristics*

*** Arterial phase hypervascularity and delayed phase "washout"**

Liver biopsy is not necessary for confirming diagnosis, but recommended if imaging criteria not met

Bruix J & Sherman M - AASLD guidelines; Hepatology 2011:53:1020-1022

DIAGNOSIS OF HCC – LIVER BIOPSY?

Biopsy not always necessary to confirm diagnosis of HCC if the lesion meets radiologic criteria in the appropriate clinical setting

- *False negative biopsy common in clinical practice and may lead to delay in diagnosis and treatment*
- *Tumor seeding along the biopsy tract in 1-5 %*

Biopsy in selected cases if atypical radiologic appearance or lack of strong risk factor for HCC

LIVER IMAGING REPORTING AND DATA SYSTEM (LI-RADS)

American College of Radiology: Standardized reporting of CT or MRI imaging for HCC in patients with cirrhosis or other risk factors

LI-RADS 1: Definite benign
LI-RADS 2: Probable benign
LI-RADS 3: Indeterminate
LI-RADS 4: Probable HCC
LI-RADS 5: Definite HCC

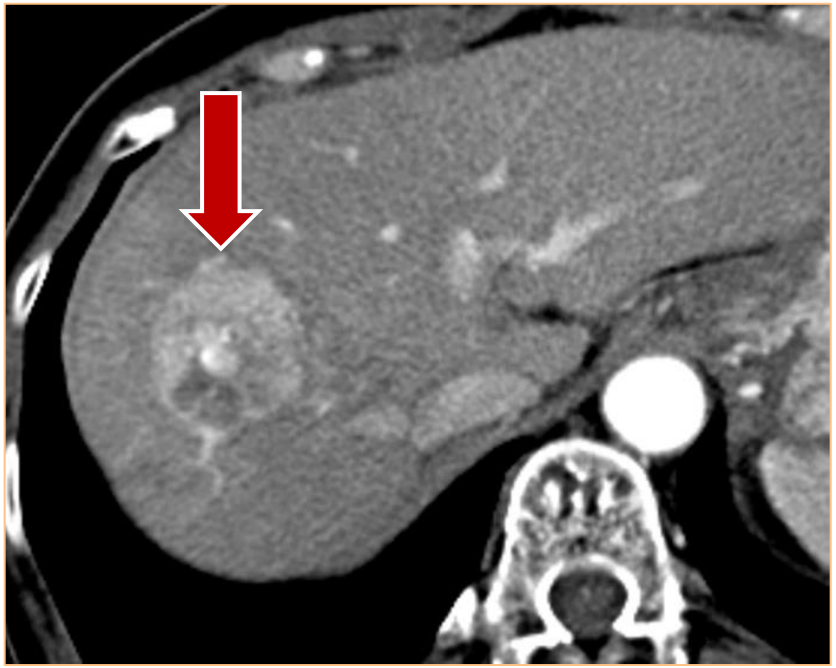
LI-RADS
MAJOR DIAGNOSTIC CRITERIA

- Arterial phase hyper-enhancement
- Delayed phase “washout”
- Pseudo-capsule
- Interval growth ≥50% within 6 months

Different diagnostic criteria for lesion ≥2 cm versus <2 cm

HCC – RADIOLOGIC DIAGNOSIS

Arterial Phase



Hyper-enhancement

Portal Venous phase

“washout”

HCC – RADIOLOGIC DIAGNOSIS

Arterial Phase **Portal Venous phase**

LIVER IMAGING REPORTING AND DATA SYSTEM (LI-RADS)

Diagnostic Criteria		LIVER MASS				
		Arterial phase hypo- or Iso-enhancement		Arterial phase hyper-enhancement		
		< 2 cm	≥ 2 cm	< 1 cm	1-1.9 cm	≥ 2 cm
"Washout" "Capsule" Threshold growth	None	LIRAD 3	LIRAD 3	LIRAD 3	LIRAD 3	LIRAD 4
	One	LIRAD 3	LIRAD 4	LIRAD 4	LIRAD 4	LIRAD 5
	≥ Two	LIRAD 4	LIRAD 4	LIRAD 4	LIRAD 5	LIRAD 5

LIVER IMAGING REPORTING AND DATA SYSTEM (LI-RADS)

Diagnostic Criteria		LIVER MASS				
		Arterial phase hypo- or Iso-enhancement		Arterial phase hyper-enhancement		
		< 2 cm	≥ 2 cm	< 1 cm	1-1.9 cm	≥ 2 cm
"Washout" "Capsule" Threshold growth	None	LIRAD 3	LIRAD 3	LIRAD 3	LIRAD 3	LIRAD 4
	One	LIRAD 3	LIRAD 4	LIRAD 4	LIRAD 4	LIRAD 5
	≥ Two	LIRAD 4	LIRAD 4	LIRAD 4	LIRAD 5	LIRAD 5

UNOS imaging criteria for HCC in determining MELD exception listing: LIRADS 5
May miss HCC with atypical features (hypo-vascular HCC)

RISING INCIDENCE OF HCC IN U.S.

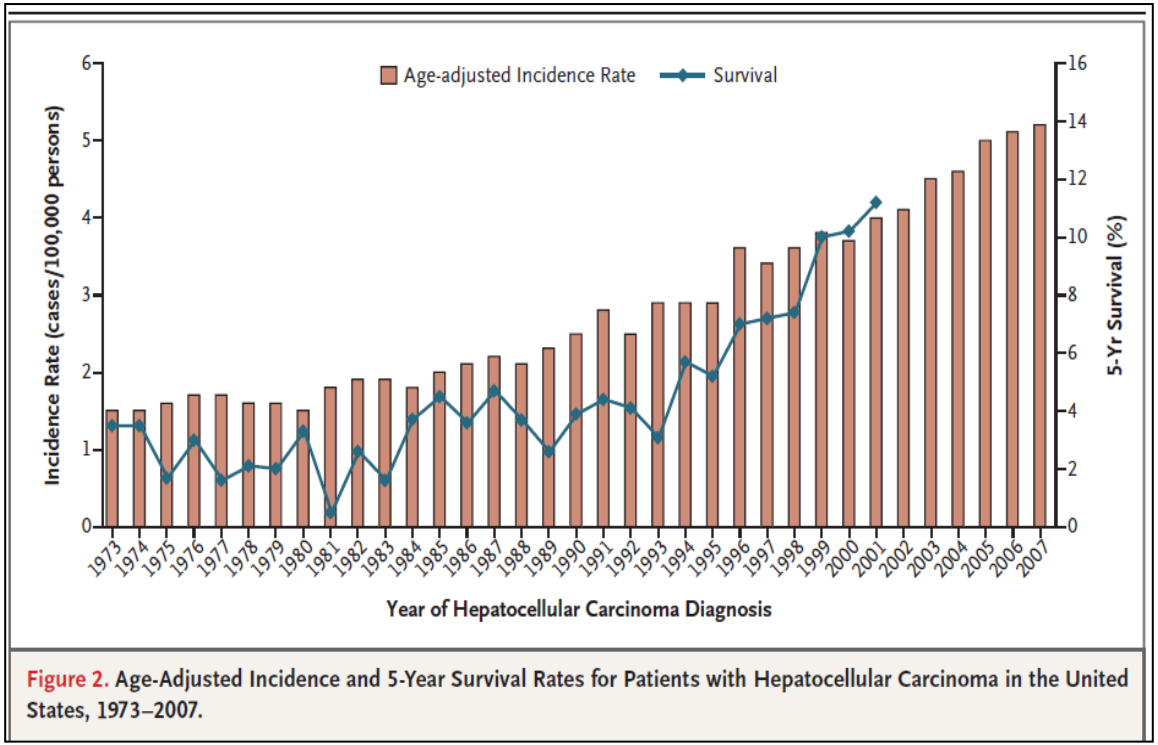


Figure 2. Age-Adjusted Incidence and 5-Year Survival Rates for Patients with Hepatocellular Carcinoma in the United States, 1973–2007.

El-Serag H. N Engl J Med 2011;365:1118-1127 (with permission)

Abstract # 166 (Parallel Session; November 10, 2014)

Hepatocellular Carcinoma Surveillance among Cirrhotic Patients with Commercial Health Insurance

David S. Goldberg[1,2]; Adriana Valderrama[3]; Rajesh Kamalakar[3]; Sujit S Sansgiry[4]; Svetlana Babajanyan[3]; James D. Lewis[1,2]

1. Division of Gastroenterology, University of Pennsylvania, PA;
2. Center for Clinical Epidemiology, University of Pennsylvania, PA;
3. Bayer HealthCare, Whippany, NJ;
4. University of Houston College of Pharmacy, TX

Introduction

- HCC occurs almost exclusively in the setting of chronic liver disease[1,2]
- Most cancers are diagnosed at advanced stage
  - Curable if diagnosed at early stage
- Since 2005, AASLD guidelines recommend HCC surveillance every 6 months for cirrhotic patients[3]
  - Based on 1 RCT and several observational studies
  - Aligned with EASL guidelines

1. Bruix J, Sherman M. *Hepatology* 2011; 53(3): 1020-22
2. El Serag HB. *N Eng J Med* 2011; 365 (12): 1118-1127
3. Bruix J, Sherman M. *Hepatology* 2005; 42(2): 1208-1236.

Introduction

- Previous population-based studies are limited to Medicare, VA, or Medicaid population[1,2,3]
  - Low HCC surveillance rates (30-40%)
  - Limited generalizability to broader population with commercial health insurance (55% US adults)
- It is unknown how frequently patients with commercial insurance receive surveillance

1. Davila JA, et al. *Annals of Internal Medicine* 2010; 52(1): 132-141
2. Palmer LB, et al. *J Clin Gastroenterol* 2013; 5: 501-512
3. Davils JA, et al. *Hepatology* 2010; 52(1): 132-141

Methods

- Data source: Truven Health Analytics Databases™
  - 100 large employers, health plans, and government and public organizations
  - Inpatient and outpatient healthcare utilization
  - Available data from 1/1/2002-12/31/2010

Inclusion criteria:

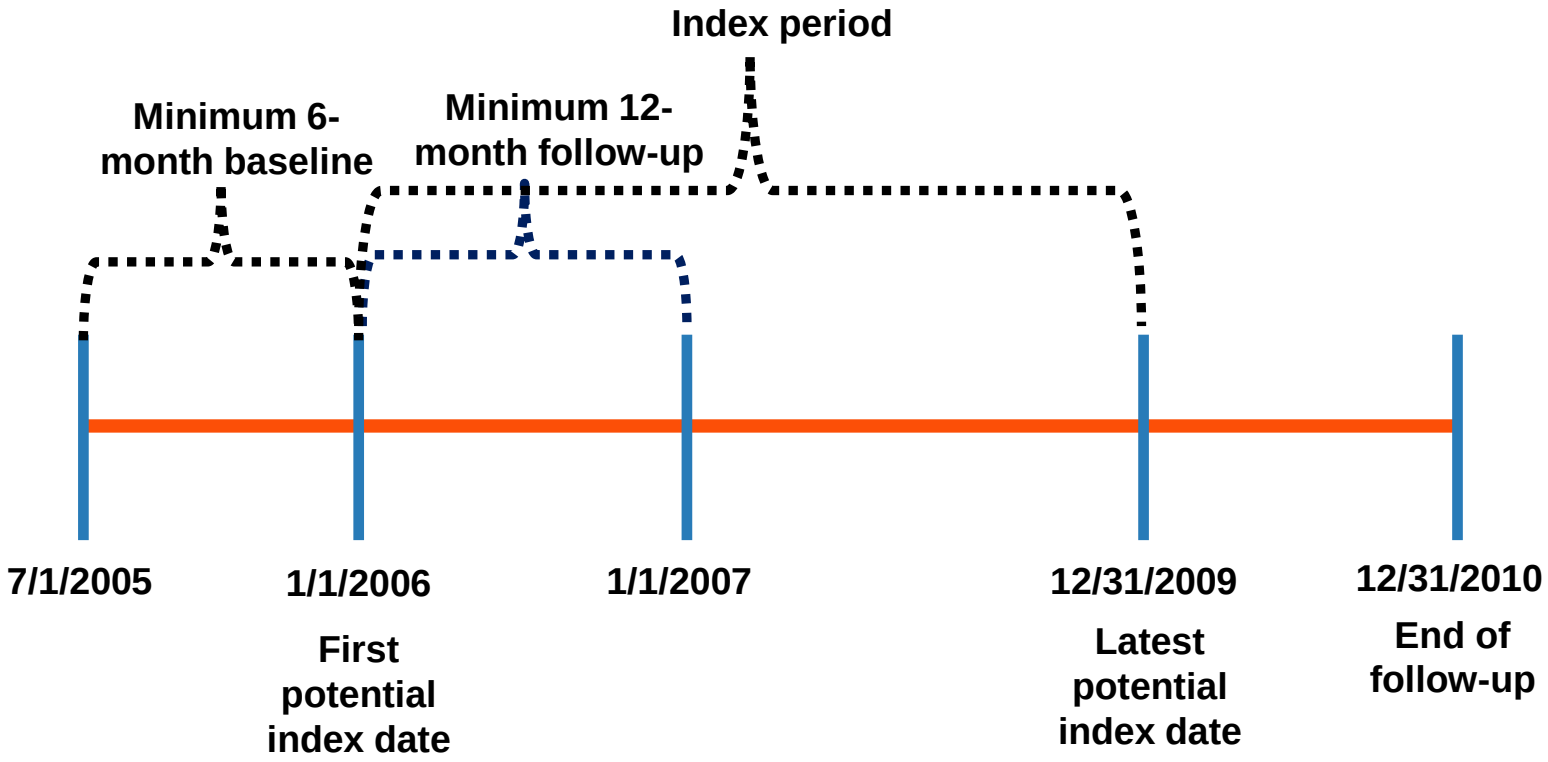
- Adults ≥18 years of age
- Cirrhosis: ICD-9-CM coding algorithm (571.2: alcoholic cirrhosis; or 571.5: cirrhosis of the liver without alcohol)[1,2]
  - One inpatient or
  - Two outpatient ICD-9-CM cirrhosis

Exclusion:

- HCC during baseline or initial 12-month period
- Malignancy in baseline or 12-months follow-up
- Liver transplant during 12-month follow-up

1. Goldberg DS, et al. *Pharmacoepidemiol Drug Saf.* 2013;22(1):103-107
2. Nehra MS, et al. *Journal of Clinical Gastroenterology* 2013; 46(5): e50-54

Methods


Index period
Minimum 6-month baseline
Minimum 12-month follow-up
7/1/2005
1/1/2006
First potential index date
1/1/2007
12/31/2009
Latest potential index date
12/31/2010
End of follow-up

Methods

- Outcomes
  - Primary: Abdominal ultrasound (CPT: 76700 or 76705)
    - Regardless of indication->any ultrasound serves as screening
  - Secondary: Contrast-enhanced CT and/or MRI
  - Outcome measures
    - Categorical: None, incomplete, complete
    - Continuous: Proportion of time up-to-date with surveillance (PUTDS)
      - 6-months “up-to-date” following each ultrasound
      - Calculated: (# months up-to-date) / (# months follow-up)
- Statistical analysis:
  - Categorical outcome: Multinomial logistic regression
  - Continuous outcome: Linear regression

Baseline Characteristics, n=8,916

Characteristics	
Median age in years, IQR	56 (50-62)
Male gender, No. (%)	5,180 (58.1)
Geographic region, No. (%)	
South	4,151 (46.6)
Northeast	837 (9.4)
North Central	2,340 (26.2)
West	1,565 (17.6)
Provider Specialty, No. (%)‡	
Gastroenterology	4,525(50.8)
Primary care/Internal Medicine	1,849(20.8)
Medical co-morbidities, No. (%)	
HIV	59(0.7)
Metabolic syndrome	6,293(70.6)
Hepatic decompensation prior to index date, N. (%)	4,553(51.1)
Etiology of liver disease identified on or prior to index date	
Alcoholic liver disease	3,798(42.6)
Hepatitis C	2,239(25.1)
Hepatitis B	511(5.7)
Alpha-1-Antitrypsin deficiency	18(0.2)
Hemochromatosis/iron overload	155(1.7)
Wilsons disease	14(0.2)
Budd-chiari syndrome	17(0.2)
Primary sclerosing cholangitis	145(1.6)
Primary biliary cirrhosis	464(5.2)
Median follow-up in months, IQR	22.93(16.17-33.87)

Categorical and Continuous Measures of HCC Surveillance

Follow-up period	Outcome				
	Categorical, N. (%)			Continuous PTUDS	
	Complete	Incomplete	None	Mean (SD)	Median (IQR)
All follow-up, n=8,916	785 (8.8)	4,943 (55.4)	3,188 (35.8)	0.34 (0.29)	0.31 (0.03-0.52)
Months 0-12, n=8,916	1,327 (14.9)	3,544 (39.8)	4,045 (45.5)	0.38 (0.33)	0.48 (0.00-0.57)
Month 13-24, n=4,071	445 (10.9)	1,168 (28.7)	2,458 (60.4)	0.25 (0.32)	0.00 (0.00-0.50)

Number of Physician Visits and HCC Surveillance Patterns

Prior hepatic decompensation	Category	Number	Mean (SD) number of physician visit
No	Complete	290	1.8 (2.3)
	Incomplete	2251	1.1 (1.6)
	None	1822	0.6 (1.2)
Yes	Complete	495	2.8 (3.4)
	Incomplete	2692	1.5 (2.1)
	None	1366	1.1 (1.8)

Multinomial Logistic Regression Model

Variable	Multivariable Odds ratio (95% CI) for Incomplete	Multivariable odds ratio (95% CI) for None	P-value
Age at cirrhosis diagnosis	1.10 (0.10-1.02)	1.02 (1.01-1.02)	0.01
Insurance plan type			0.04
PPO/POS	Reference	Reference	
HMO	0.83 (0.65-1.06)	0.90 (0.70-1.17)	
Comprehensive	0.94 (0.68-1.30)	1.11 (0.80-1.53)	
Other*	3.53 (1.41-8.88)	3.60 (1.42-9.18)	
Provider specialty			<0.001
Gastrointestinal	Reference	Reference	
Primary care/Internal Medicine	1.11 (0.89-1.40)	1.83 (1.46-2.30)	
Internal medicine subspecialty	1.91 (0.85-4.31)	2.55 (1.12-5.80)	
Other provider type	1.20 (0.92-1.58)	1.82 (1.38-2.40)	
Prior hepatic decompensation	0.78 (0.64-0.95)	0.51 (0.41-0.62)	<0.001
≥1 component metabolic syndrome	0.78 (0.64-0.96)	0.77 (0.63-0.96)	0.05
Hepatitis C	0.91 (0.75-1.10)	0.69 (0.56-0.84)	<0.001

* Other insurance subtype: consumer-directed, high-deductible, capitated point-of-service, or equivalent premium income health insurance

Conclusions

- HCC surveillance rates for commercially insured patients with cirrhosis remains poor despite formalized HCC surveillance guidelines
- Access to care variables are associated with surveillance rates
  - Even among those with favorable characteristics, surveillance rates are lower than expected
- Surveillance rates are highest in the first year of eligibility, with decline in subsequent years

Limitations

- Only determine if an ultrasound was performed, and not whether it was ordered but never completed
- Patient factors (compliance)
- Could not distinguish between incident (new diagnosis) versus prevalent (diagnosis before) cases of cirrhosis
- Surveillance every 6 or 12 months considered acceptable in previous practice guidelines

Abstract # 232 (Parallel Session; November 11, 2014)

Incidence of Hepatocellular Carcinoma in a US Cohort of Chronic Hepatitis B Patients by Age, Gender, Cirrhosis and Antiviral Treatment Status

Derek Lin[1]; Nghia Nguyen[2]; Joseph Hoang[1]; Vinh Vu [1]; Huy Trinh[3]; Jiayi Li[4]; Jian Zhang[5]; Huy Nguyen[3]; Khanh Nguyen[3]; Mindie Nguyen[1]

1. Stanford University Medical Center, Palo Alto, CA;
2. University of California, San Diego, CA;
3. San Jose Gastroenterology, San Jose, CA;
4. Palo Alto Medical Foundation, Mountain View, CA
5. Chinese Hospital, San Francisco, CA

Background

- Studies from Asia and Europe have indicated reduced risk of HCC with treatment.
- In the US, the Chronic Hepatitis Cohort Study (CHeCS) also observed reduced HCC risk in treated patients.

Gordon SC, Lamerato LE, Rupp LB, et al. Clin Gastroenterol Hepatol 2014;12:885-93.
Lai CL, Yuen MF. Hepatology 2013; 57: 399–408.
Sung JJ, Tsoi KK, Wong VW, et al. Aliment Pharmacol Ther 2008; 28:1067-1077.
Papatheodoridis GV, Lampertico P, Manolakopoulos, S, et al. J Hepatol 2010:53, 348-356.

Objective

- To examine the effect of anti-viral therapy for CHB on HCC incidence in a large San Francisco Bay Area cohort stratified by major HCC risk factors:
  - Age (< 45 or ≥45)
  - Gender
  - Cirrhosis Status

Methods

- Retrospective cohort study of 3933 consecutive CHB identified by International Classification of Disease 9 (ICD-9) codes and verified by chart review.
- Study Period: 1991 to 2014
- Study Locations: 4 centers in the San Francisco Bay Area: two medical centers - Stanford University Medical Center and Chinese Hospital and two specialty community-based clinics - San Jose Gastroenterology and Palo Alto Medical Foundation.

Methods

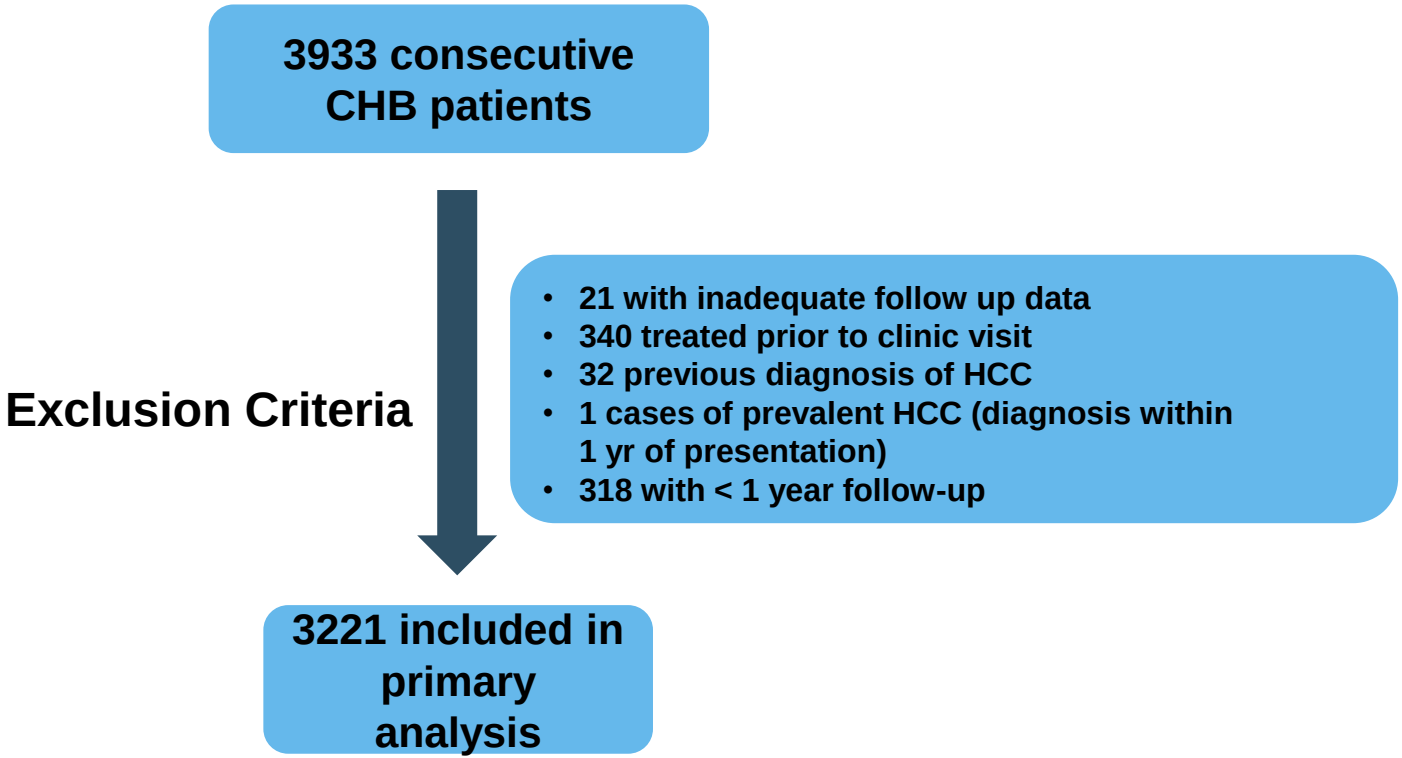
Cirrhosis:

- Liver biopsy or imaging or
- Secondary criteria:
  - ascites, encephalopathy, splenomegaly, varices, or thrombocytopenia (platelet < 120,000/uL) with liver dysfunction

HCC:

- Liver biopsy or
- Radiographic evidence per AASLD guidelines (both 2005 and 2011)

Methods


3933 consecutive CHB patients
Exclusion Criteria
21 with inadequate follow up data
340 treated prior to clinic visit
32 previous diagnosis of HCC
1 cases of prevalent HCC (diagnosis within 1 yr of presentation)
318 with < 1 year follow-up
3221 included in primary analysis

Baseline Patient Characteristics

	Overall Cohort n=3221	Not Treated n=1983	Treated n=1238	*p*-value
Age (years)	45.4 ± 13.2	45.7 ± 13.01	44.9 ± 13.5	0.14
Sex (male)	58.7%	54.5%	65.6%	<0.0001
Ethnicity				
Asian	**94.6%**	**93.4%**	**97.8%**	
Caucasian	1.4%	1.7%	0.7%	
Black	0.3%	0.3%	0.5%	
Hispanic	0.3%	0.4%	0%	
Other	3.2%	4.2%	1.1%	
Family history HBV	30.1%	29%	30%	<0.0001
Family history HCC	12.8%	11.9%	12.9%	<0.0001
Smoking history	19.2%	16.9%	22.7%	<0.0001
Alcohol history	26.8%	23.4%	31.9%	<0.0001

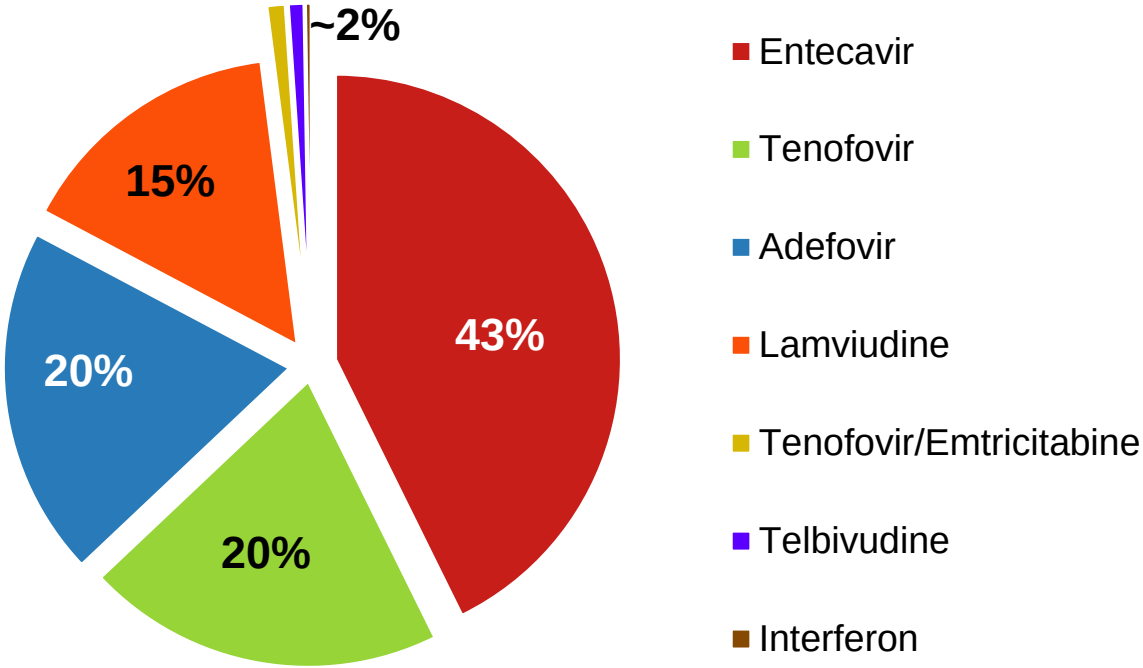
Baseline Patient Characteristics

	Overall Cohort n=3221	**Not Treated n=1983**	**Treated n=1238**	***p*-value**
Median follow up time	49 (12 – 206)	44 (12 – 206)	53 (12 – 161)	0.30
Cirrhosis (yes)	8.7%	9.2%	7.9%	0.20
Positive HBeAg	25.5%	17.4%	39.9%	<0.0001
HBV DNA (log_{10} IU/mL)	4.49 (0.0 - 11.99)	3.59 (0 .0 - 11.99)	5.5 (0.0 – 11.3)	<0.00001
ALT (U/L)	38 (2.5 - 4000)	31 (2.5 – 4000)	55 (4 – 2809)	<0.0001

Treatment and HCC Development

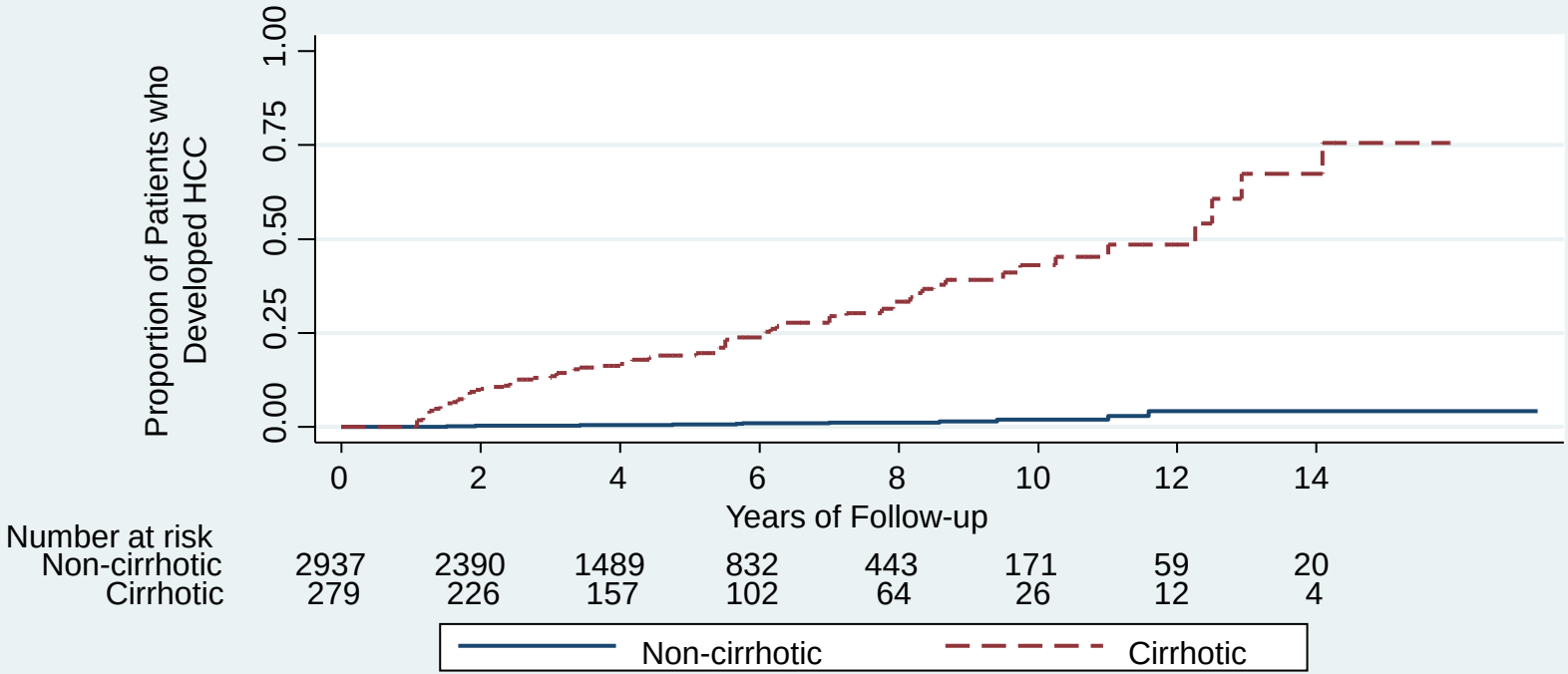
- Most patients did not receive treatment (61.6%).
- Those that were treated mostly achieved viral suppression (86.9%).
- A total of 102 (3.2%) patients ultimately developed HCC.

Anti-HBV Medications



HCC Incidence, by Cirrhosis Status

6.6 cases per 1000 person years (53.97 cirrhotics, 1.57 non-cirrhotics)

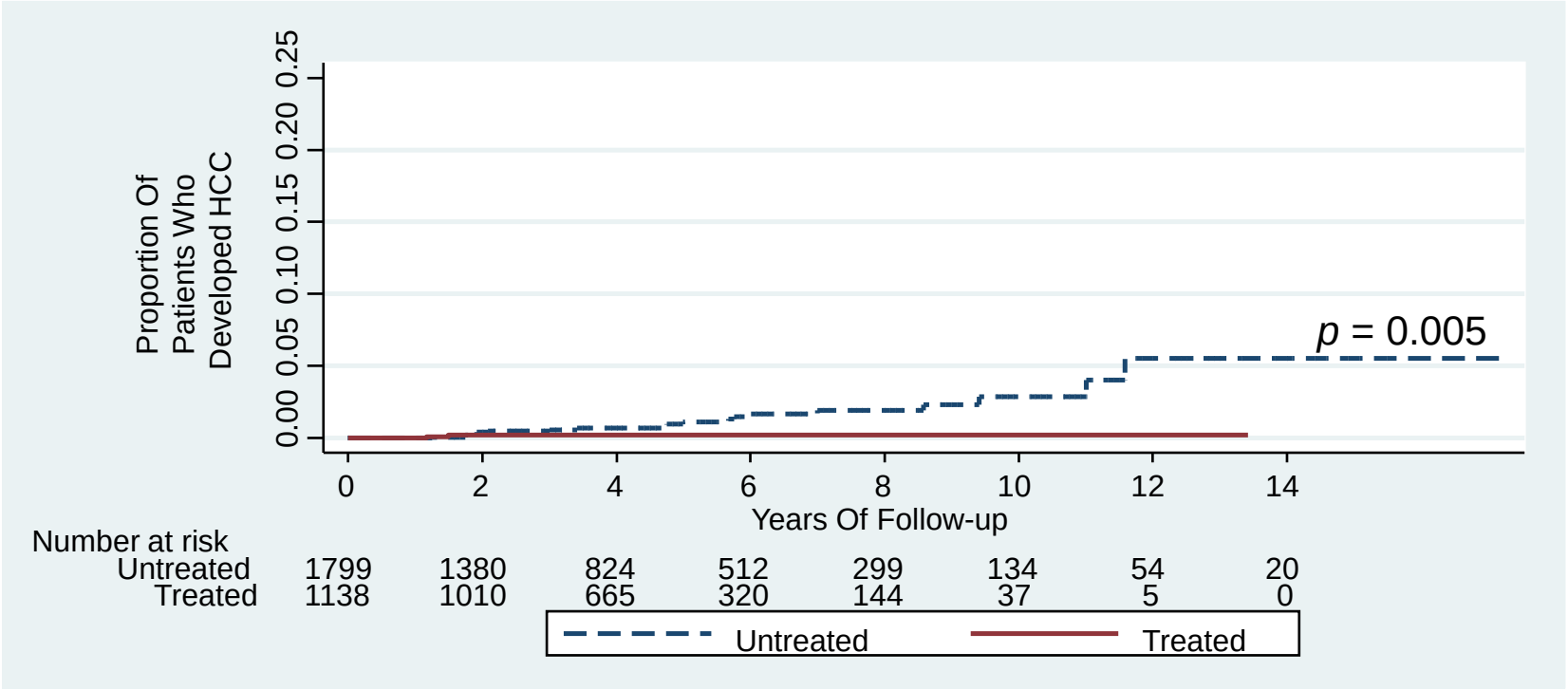


HCC Incidence, in Patients with Cirrhosis by Treatment

6.6 cases per 1000 person years (53.97 cirrhotics, 1.57 non-cirrhotics)

HCC Incidence, in Patients without Cirrhosis by Treatment

6.6 cases per 1000 person years (53.97 cirrhotics, 1.57 non-cirrhotics)



Predictors of HCC

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	***p*-value**	**HR (95% CI)**	***p*-value**
Male	3.4 (2.1-5.7)	<0.0001	2.8 (1.5-5.2)	0.001
≥45 years (vs <45 years)	4.8 (2.9-7.9)	<0.0001	2.8 (1.5-4.9)	0.001
Cirrhosis (vs non-cirrhosis)	29.9 (18.9-47.3)	<0.0001	17.3 (10.1-29.8)	<0.0001
Treated (vs untreated)	0.28 (0.16-0.49)	<0.0001	0.43 (0.23-0.79)	0.007
HBeAg-positivity	0.77 (0.47-1.27)	0.31	1.1 (0.63-1.97)	0.70
ALT* ≥2x ULN (vs ALT <2x ULN)	1.18 (0.79-1.78)	0.42	1.07 (0.67-1.71)	0.77
HBV DNA ≥20,000 (vs <20,000 IU/mL)	0.82 (0.54-1.22)	0.32	0.81 (0.50-1.3)	0.39

*ALT ULN cut off values were < 30 IU/L in *men* < 19 IU/L in *women*

Conclusions

- HCC incidence was significantly lower in patients with anti-HBV treatment among both non-cirrhotic and cirrhotic patients.

- Antiviral therapy was a significant independent predictor for decreased HCC risk in our mostly Asian cohort of 3221 CHB patients regardless of age, sex, or cirrhosis status

Conclusions

- However, HCC still develops at a significantly high rate in treated patients especially in older men and patients with cirrhosis.

- HCC surveillance should be continued in patients regardless of treatment status.

Limitations

- Retrospective study design
- It has already been shown in a RCT that treatment of CHB (LAM) in cirrhotics reduces the risk for HCC
- Low incidence of HCC in the non-cirrhotic group, difficult to ascertain the benefit of anti-viral therapy in risk reduction

Liaw YF, et al. N Engl J Med. 2004;351:1567

Liver Transplant for HCC

- The Milan criteria (1 lesion ≤ 5 cm, 2-3 lesions ≤ 3 cm) remain the "gold standard" for the selection of liver transplant (LT) candidates

- Currently only patients with HCC meeting UNOS T2 criteria (1 lesion 2-5 cm, 2-3 lesions < 3 cm) are eligible for priority listing with MELD exception for LT. Patients with T1 HCC (1 lesion < 2 cm) are not eligible for MELD exception

- Local regional therapy (LRT) is commonly used to control tumor growth especially in regions with long waiting time, serving as a bridge to LT

Mazzaferro et al. N Engl J Med 1996;334: 693-699

Abstract # 111 (Presidential Plenary Session; November 10, 2014)

Multicenter Study of Down-Staging of Hepatocellular Carcinoma (HCC) to Within Milan Criteria Before Liver Transplantation

Neil Mehta[1]; Jennifer Guy[2]; Catherine T. Frenette[3]; Monika Sarkar[1]; Robert W. Osorio[2]; William B. Minteer[3]; John P. Roberts[1]; Francis Y. Yao[1]

1. University of California, San Francisco; 2. California Pacific Medical Center, San Francisco; 3. Scripps Clinic, San Diego

region 5

UCSF Transplant

CPMC Sutter Health

Scripps

Background

- Down-staging of HCC is a process involving expanded liver transplant criteria and the effects of local-regional therapy
- Definition of down-staging: Reduction in the size of tumor(s) using local regional therapy to meet acceptable liver transplant criteria
- Tumor response to down-staging treatment is based on radiographic measurement of the size of viable tumors

Yao FY, et al, Liver Transpl 2011; Ravaioli et al. Am J Transpl 2008; Pomfret et al. Liver Transplant 2010; Bruix, J et al EASL Practice Guidelines, J Hepatology 2012

Background

- Single center studies have reported excellent post-LT outcomes for selected patients following successful down-staging to Milan criteria

- In one study from UCSF, a down-staging group undergoing LT (n=68) had similar intention-to-treat survival and post-transplant survival compared to patients with initial HCC meeting T2 criteria who underwent LT over the same time period (n=332)

Yao et al. Hepatology 2012;56 (Suppl);211A (AASLD 2012)

Multi-Center Study Rationale and Aim

- The UCSF down-staging protocol has been adopted by Region 5; but post-LT outcomes have not yet been reported from other Region 5 centers
- No multicenter down-staging studies have been reported in the literature to date
- This multicenter study from 3 Region 5 centers aimed to assess post-LT and intention to treat outcomes under a uniform down-staging protocol

Region 5 Down-Staging Protocol

- Inclusion criteria
  - 1 lesion > 5 cm and ≤ 8 cm
  - 2 or 3 lesions, each ≤ 5 cm with total tumor diameter of all lesions ≤ 8 cm
  - 4 or 5 lesions, none >3 cm with total tumor diameter of all lesions ≤ 8 cm
  - No vascular invasion on imaging

Yao et al. Hepatology 2008;48:819-827

Region 5 Down-Staging Protocol
Additional Guidelines

- Candidates can undergo deceased-donor LT 3 months after down-staging if within Milan criteria
- Candidates can undergo LDLT 3 months after down-staging if within UCSF criteria - 1 lesion ≤6.5cm or 2-3 lesions ≤4.5cm with total tumor diameter ≤8cm
- Patients with acute hepatic decompensation after down-staging must meet criteria for successful down-staging before LT

Yao et al. Hepatology 2008;48:819-827

Patients and Methods

- 187 consecutive adult patients with HCC treated under Region 5 down-staging protocol from 3 centers (UCSF, CPMC, Scripps) from 2002-2012
- Successful down-staging: residual tumor(s) within Milan criteria
- Competing risks (CR) analysis was used to determine cumulative probabilities and predictors of dropout from the waiting list and HCC recurrence

Baseline Characteristics (N=187)

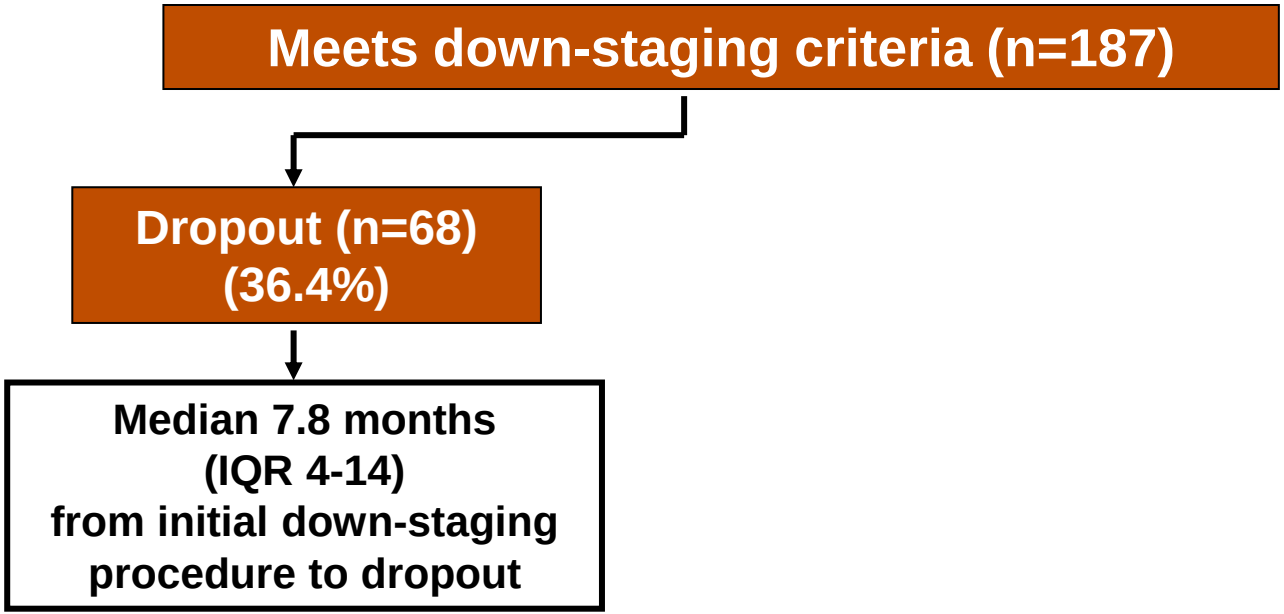
Median Age (years)	**58 (IQR 54-63)**
Male Gender	**153 (82%)**
Race/Ethnicity **Caucasian** **Asian** **Hispanic** **African American**	 **81 (43%)** **67 (37%)** **21 (11%)** **13 (7%)**
Etiology of Liver Disease **HCV** **HBV** **Other**	 **106 (57%)** **46 (25%)** **35 (18%)**
Median Child-Pugh (CP) score **CP A** **CP B** **CP C**	**7 (IQR 5-8)** **107 (57%)** **60 (32%)** **20 (11%)**

Baseline Tumor Characteristics and Treatment (N=187)

# of Lesions	N (%)	Median Size of Largest Lesion
1	71 (38%)	6.0 cm (IQR 5.7-6.7)
2-3	96 (51%)	4.0 cm (IQR 3.5-4.7)
4-5	20 (11%)	2.3 cm (IQR 2.0-2.7)

Median AFP (ng/ml) AFP >100 AFP >500	24 (IQR 8-154) 55 (29%) 29 (16%)
# of LRTs Received 1 2 3 ≥4	 48 (26%) 52 (28%) 38 (20%) 49 (26%)
Type of LRT Received TACE RFA Combination	 94 (50%) 12 (6%) 81 (43%)

Results: Dropout From Waiting List



Dropout from Waiting List

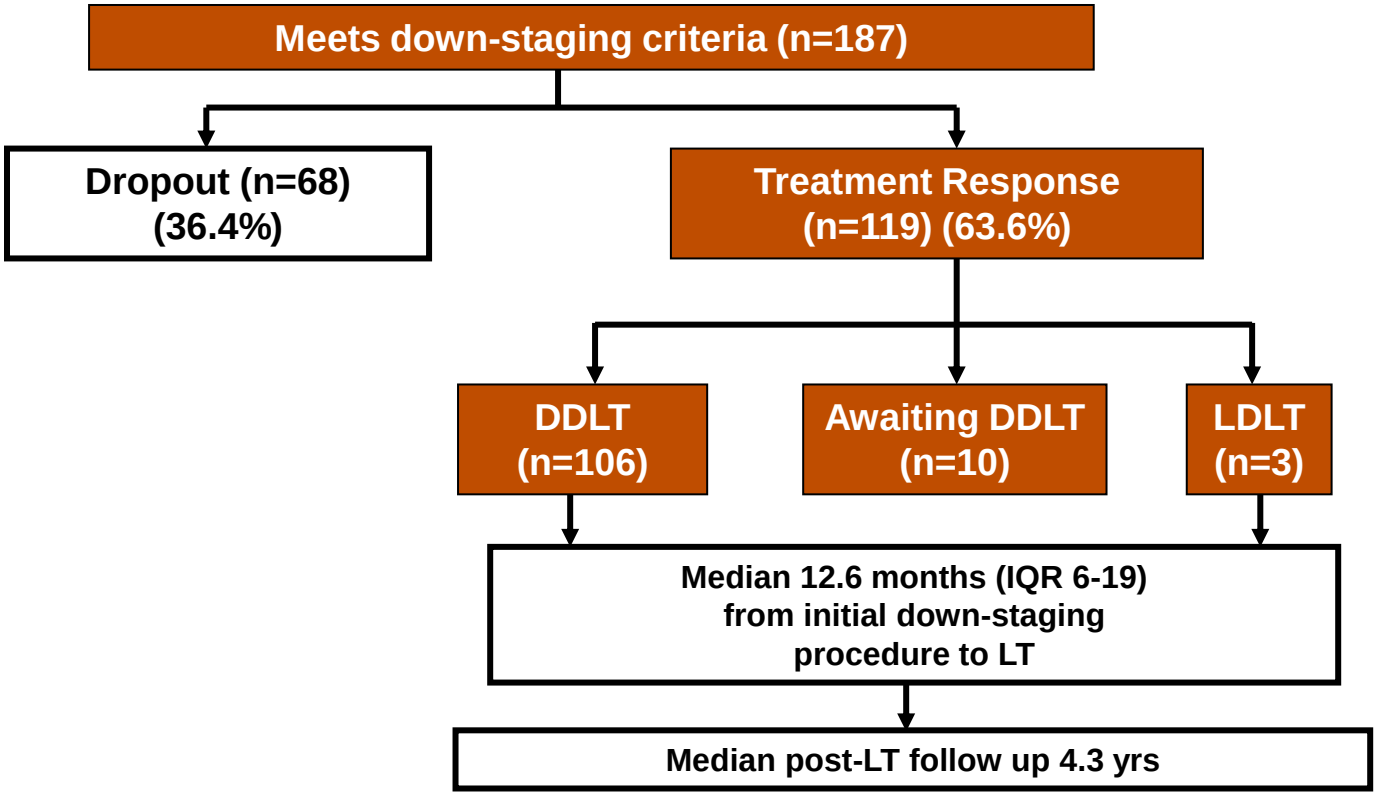
- Competing risks cumulative probability of dropout from 1st down-staging procedure → 26% at 1 year and 41% at 2 years

Predictor of Dropout	Univariate HR (95% CI)	p-value	Multivariate HR (95% CI)	p-value
Child's C vs A	2.2 (1.04-4.7)	0.04	3.2 (1.4-7.3)	0.005
Child's B vs A	1.9 (1.1-3.1)	0.02	1.9 (1.1-3.3)	0.02
Pre-treatment AFP >100*	1.9 (1.1-3.2)	0.01	NS	

***Pre-treatment AFP both as a continuous variable and at all additional tested cutoffs (>300, >400, >500, >1000) were all significant on univariate but not multivariate analysis**

Age, race/ethnicity, etiology of liver disease, and type and number of LRT received were not significant predictors of dropout

Results: Successful Down-staging



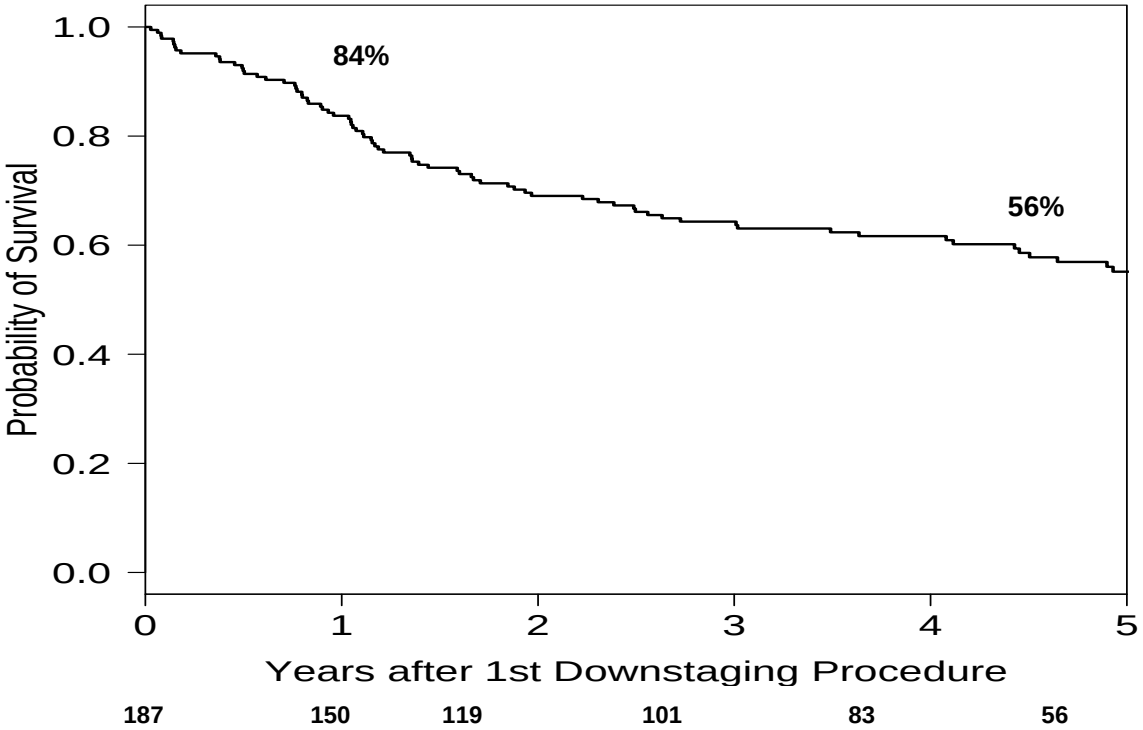
Explant Tumor Characteristics

Pathologic Tumor Stage (N=109)	**# of Patients**
Complete Necrosis	38 (35%)
Within Milan Criteria	50 (46%)
Beyond Milan Criteria (T3/T4a)	19 (17%)
Macro-vascular invasion (T4b)	1 (1%)
Lymph node invasion	1 (1%)

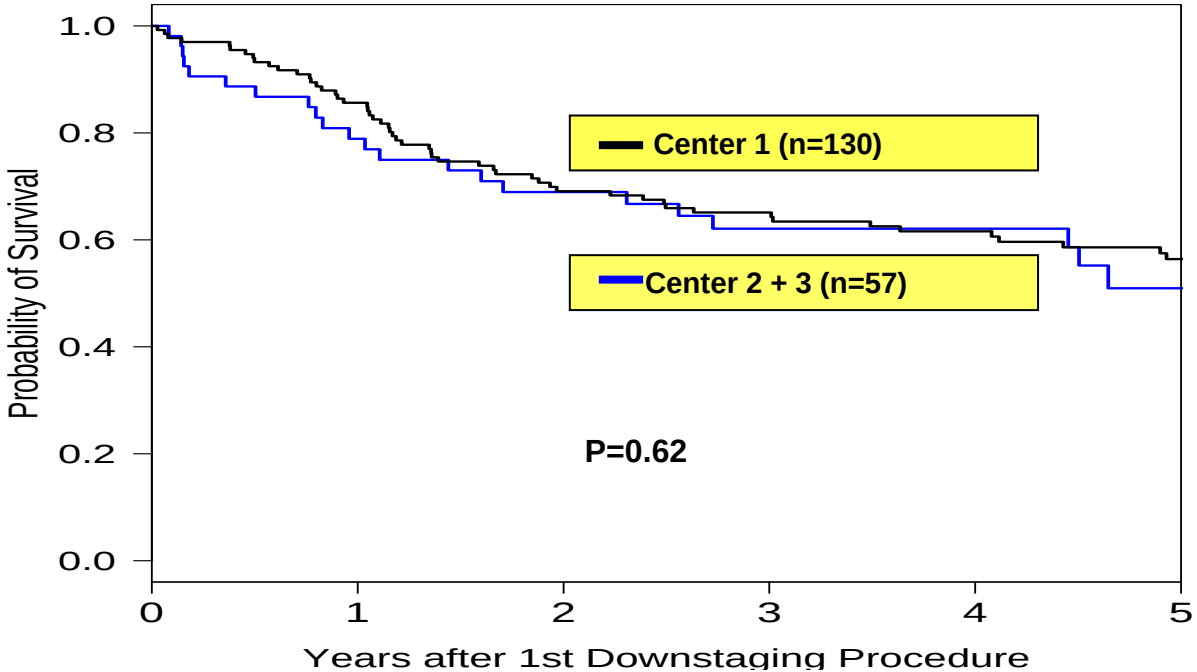
Histologic Grade (N=71)	
Well-differentiated	25 (35%)
Moderately-differentiated	45 (63%)
Poorly-differentiated	1 (1%)

Vascular invasion (N=109)	
Micro-vascular	7 (6%)
Macro-vascular	1 (1%)

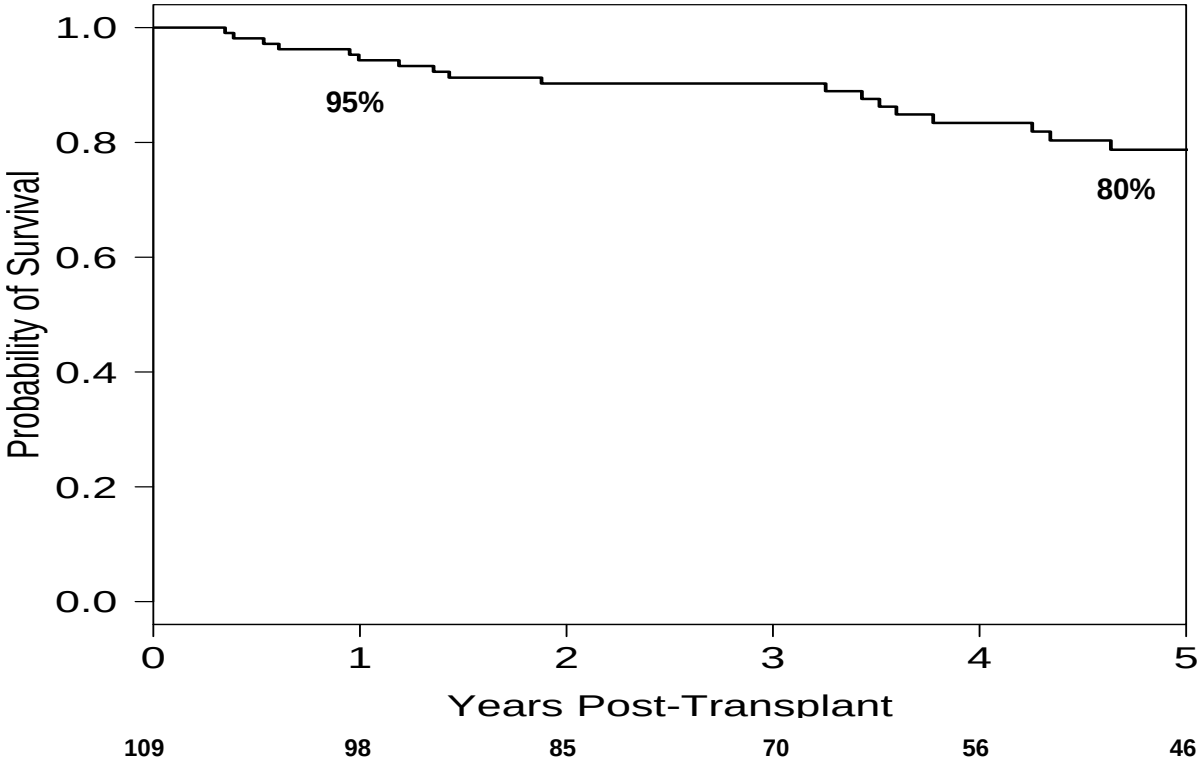
Intention-To-Treat Survival



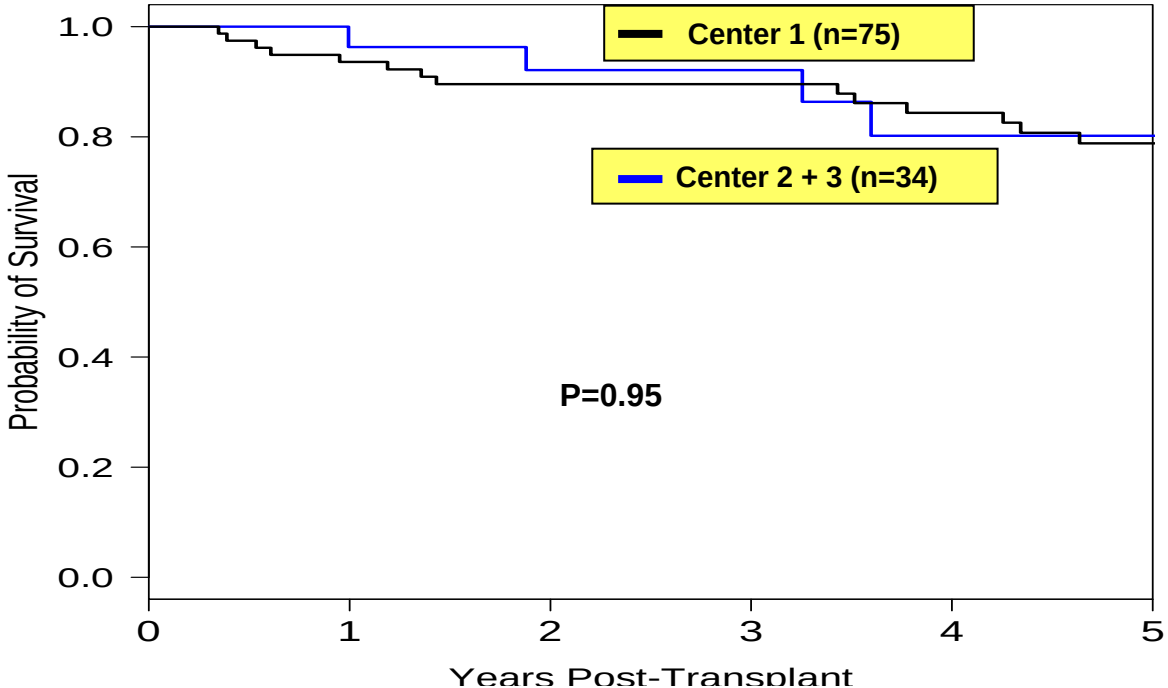
Center Specific Differences in Intention-to-Treat Survival



Post-Transplant Survival

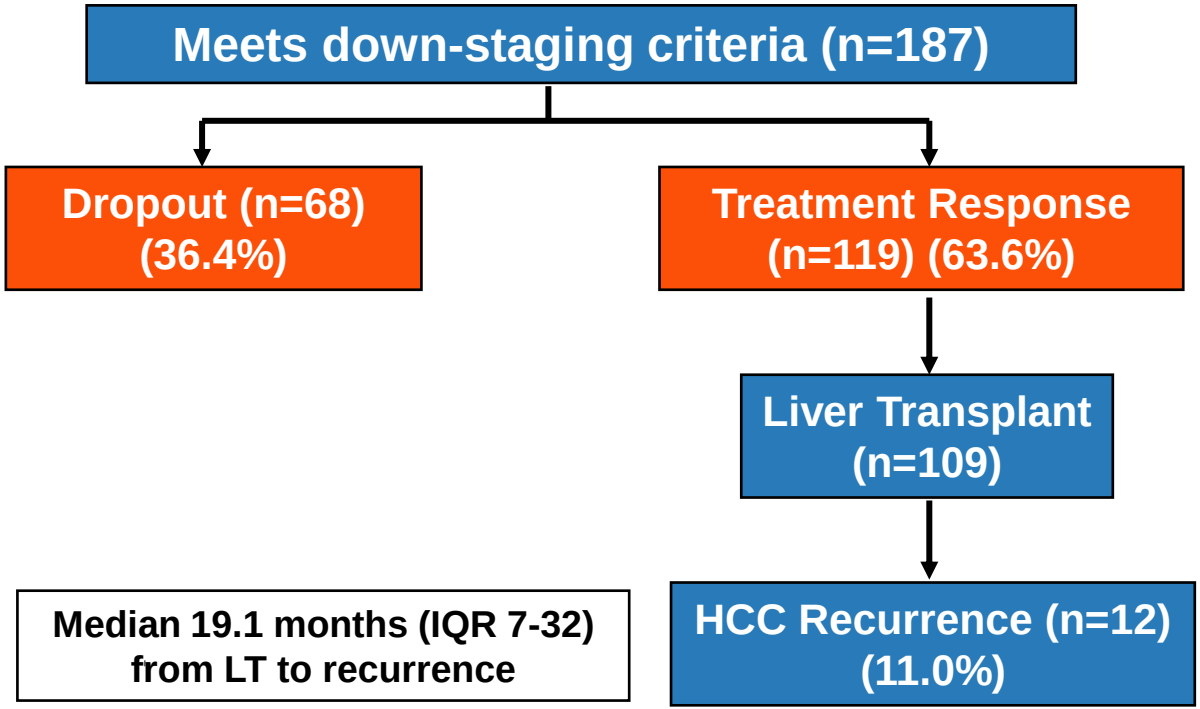


Center Specific Differences in Post-Transplant Survival

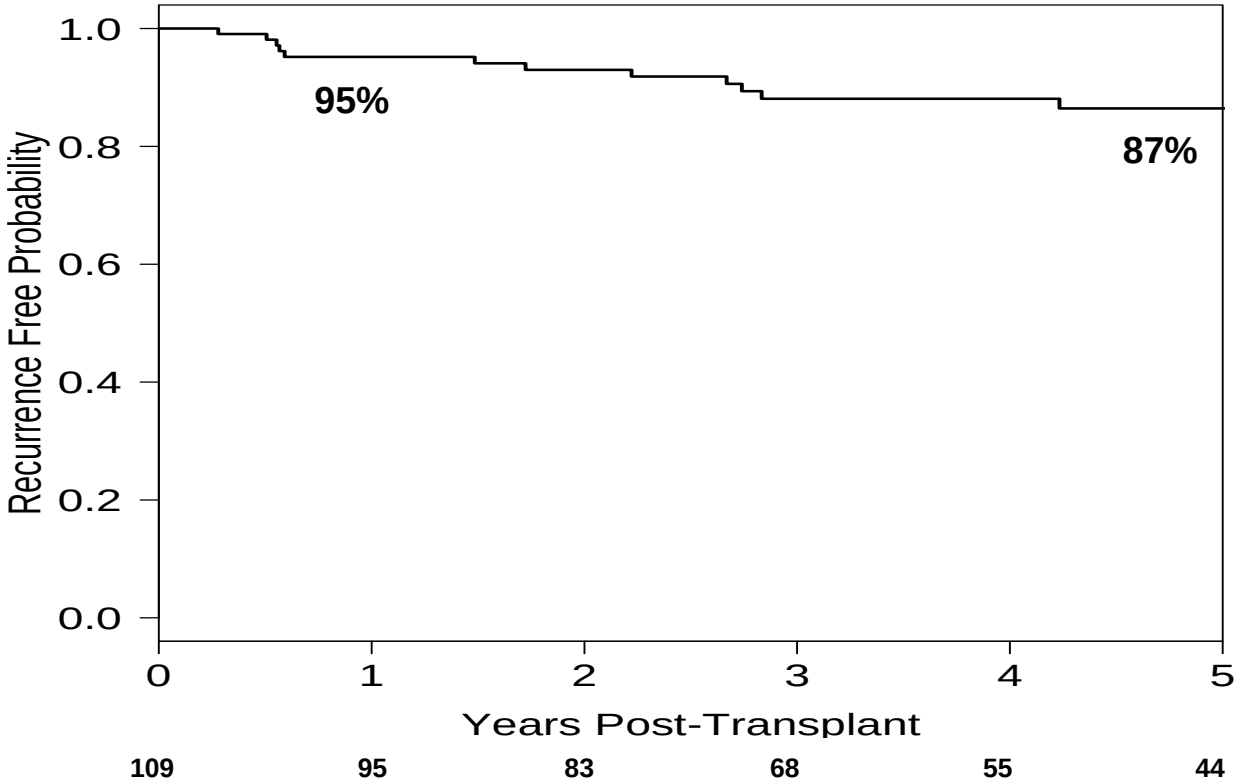


Center 1	75	71	63	53	44	38
Center 2/3	34	27	22	17	12	8

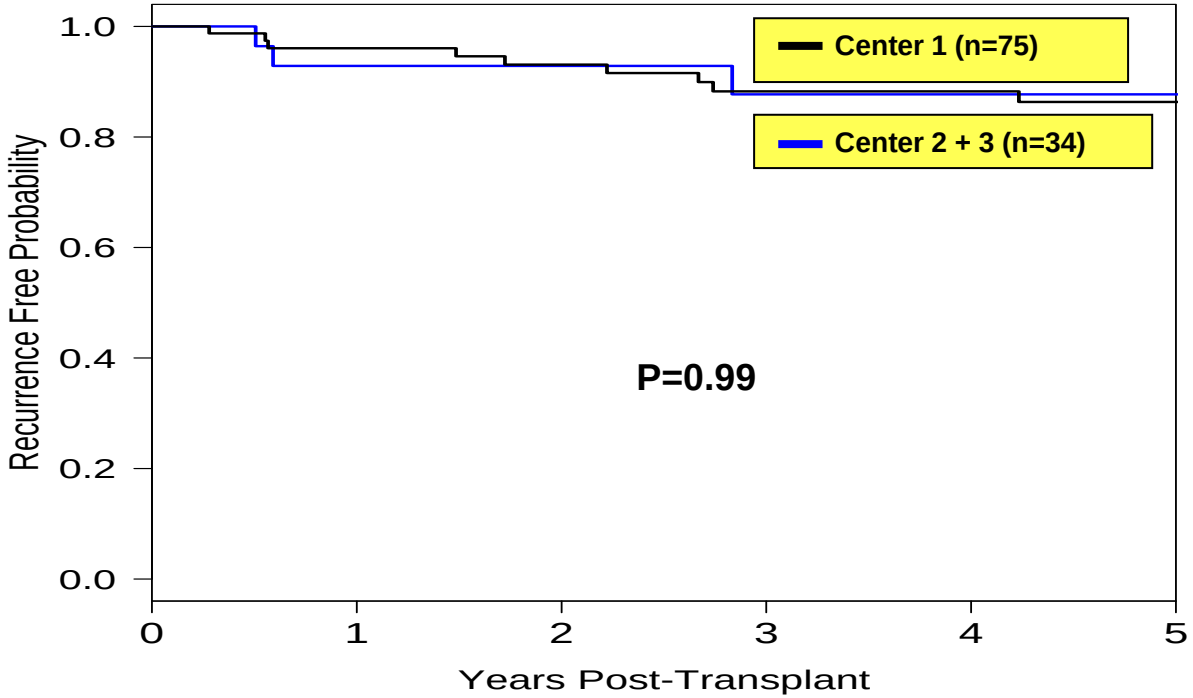
Results: HCC Recurrence



Recurrence-Free Probability



Center Specific Differences in Recurrence-Free Probability



Center 1	75	71	62	52	45	37
Center 2/3	34	24	21	16	10	7

Predictors of HCC Recurrence (Competing Risks)

Predictor of Recurrence	Univariate HR (95% CI)	p-value	Multivariate HR (95% CI)	p-value
AFP > 300	4.9 (1.5-15.5)	0.006	NS	
AFP > 400	5.4 (1.7-17.0)	0.004	NS	
AFP > 500	6.6 (2.1-21.0)	0.001	8.4 (2.0-35.6)	0.003
Microvascular invasion	3.4 (0.7-15.4)	0.11	7.3 (1.4-37.7)	0.02

Age, race/ethnicity, etiology of liver disease, type and number of LRT received, explant pathologic stage and tumor grade were not significant predictors of recurrence

Summary

- Successful down-staging to Milan criteria was achieved in nearly 2/3 of patients

- Child-Pugh class B and C were the only significant predictors of dropout due to tumor progression or death

Summary

- Successful tumor down-staging:
  - Favorable explant tumor characteristics
  - 5 year post-transplant survival of 80%
  - 5 year recurrence-free probability of 87%
- No center specific differences were found in this multi-center study
- Predictors of HCC recurrence included AFP > 500 and micro-vascular invasion

Conclusions

- In this largest series to date and first multicenter study on down-staging under a uniform protocol, we observed excellent post-transplant outcomes

- These results support broader application of this uniform down-staging protocol

Limitations

- Possible referral bias (only those with good liver function were referred for consideration of tumor down-staging)
- The benefits of tumor down-staging is unclear in patients with Child’s C cirrhosis
- Regional differences (long waiting time, high proportion of HBV and low NAFLD)