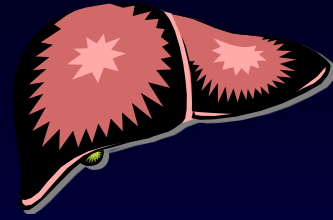
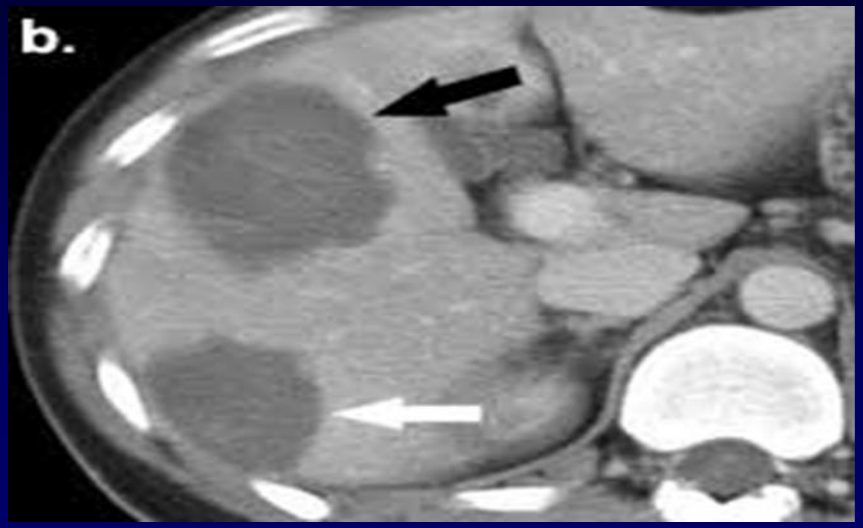
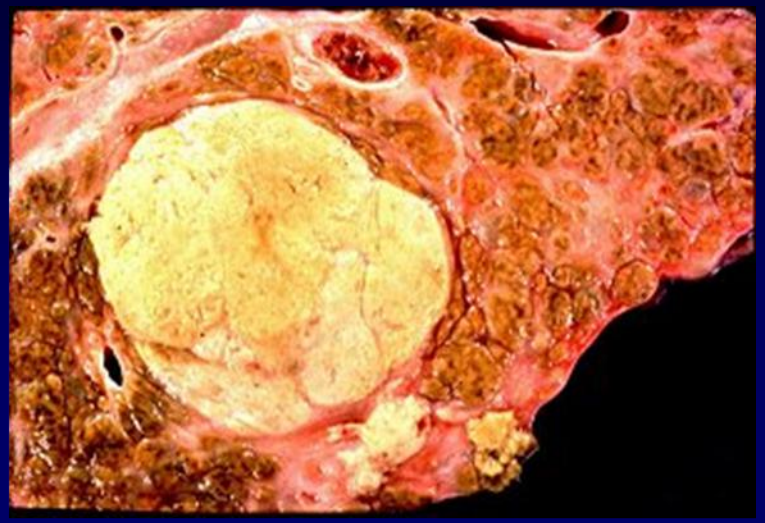
# HCC: Tumor markers





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**Liver Unit, Department of Gastroenterology and Liver Disease, Tel-Aviv Sourasky Medical Center**

**March 2016**

“Ca


Donald J. Trump
@realDonaldTrump
It's freezing and snowing in New York--
we need global warming!
1:24 PM - 7 Nov 2012
2,257
896

3

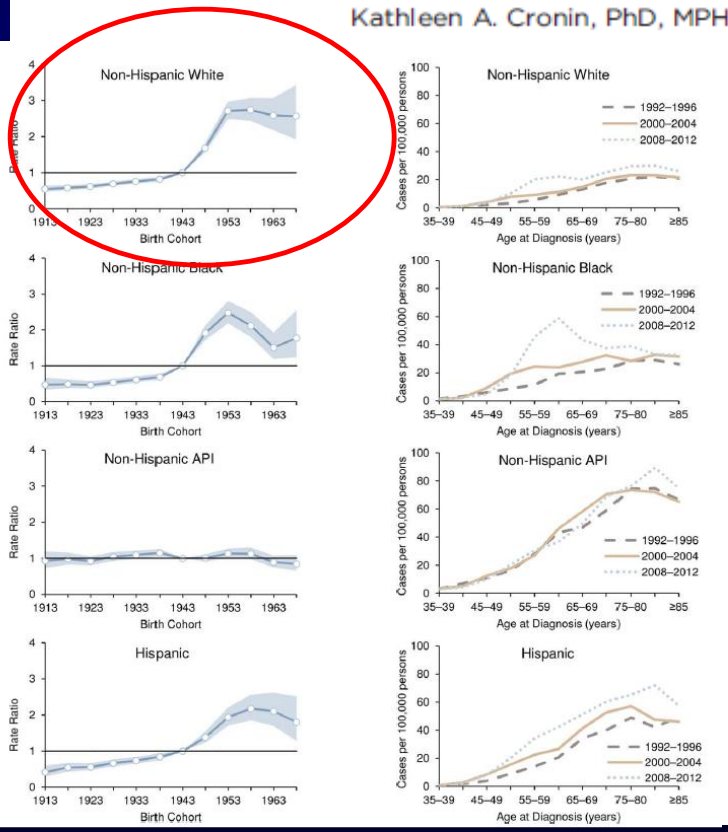
# Overview

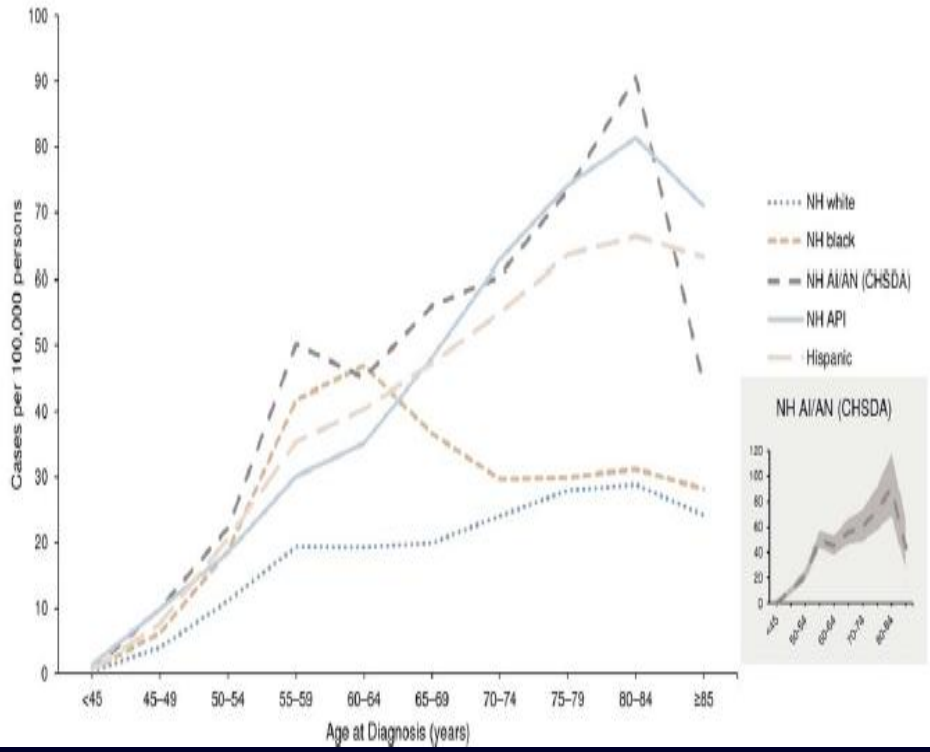
- Epidemiology of HCC-1 min
- Surveillance guidelines-1min
- Current Markers for HCC-6 min
- The future-1 min
- Summary-1 min

# Trends in Incidence and Death Rates 1994-2015

## Annual Report to the Nation on the Status of Cancer, 1975-2012, Featuring the Increasing Incidence of Liver Cancer

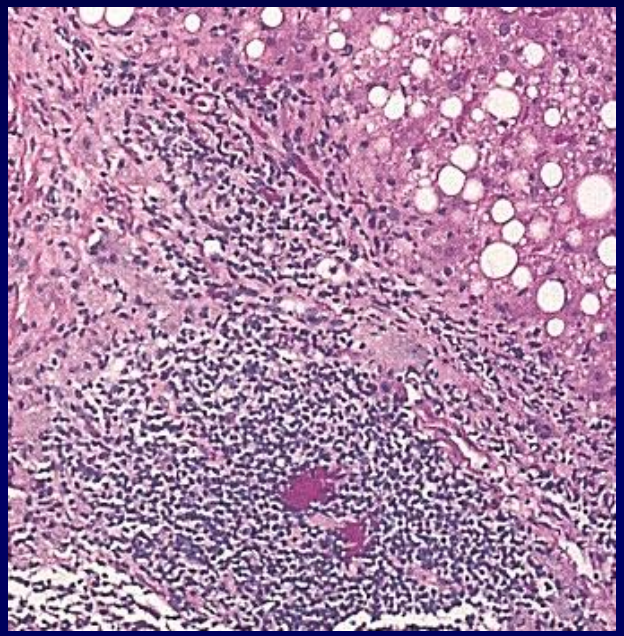
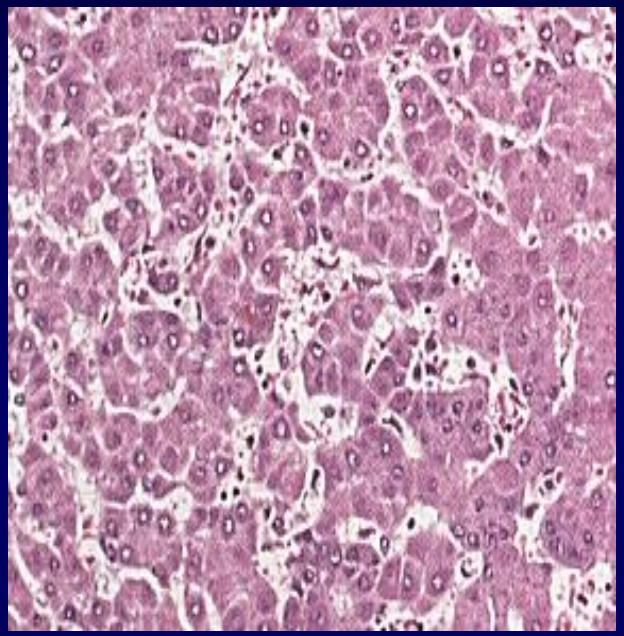
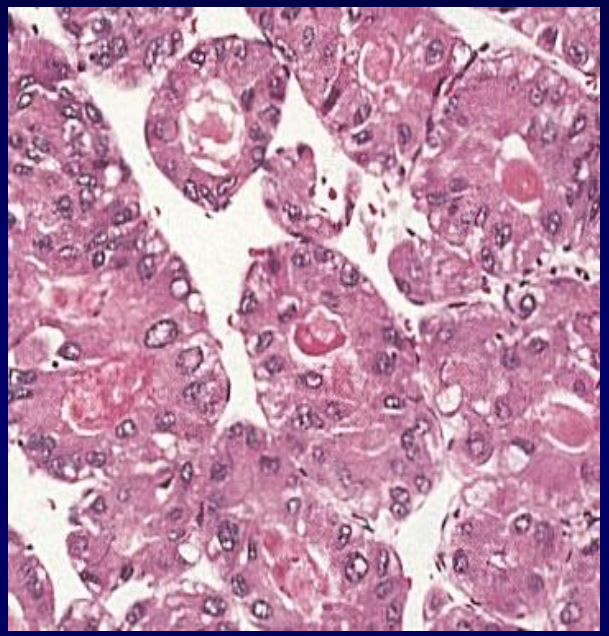
A. Blythe Ryerson, PhD, MPH[1]; Christie R. Eheman, PhD, MSHP[1]; Sean F. Altekruse, DVM, MPH, PhD[2]; John W. Ward, MD[3]; Ahmedin Jemal, DVM, PhD[4]; Recinda L. Sherman, MPH, PhD, CTR[5]; S. Jane Henley, MSPH[1]; Deborah Holtzman, PhD[3]; Andrew Lake, BS[6]; Anne-Michelle Noone, MS[2]; Robert N. Anderson, PhD[7]; Jiemin Ma, PhD, MHS[4]; Kathleen N. Ly, MPH[3]; Kathleen A. Cronin, PhD, MPH[2]; Lynne Penberthy, MD, MPH[2]; and Betsy A. Kohler, MPH[5]




www.seer.cancer.gov

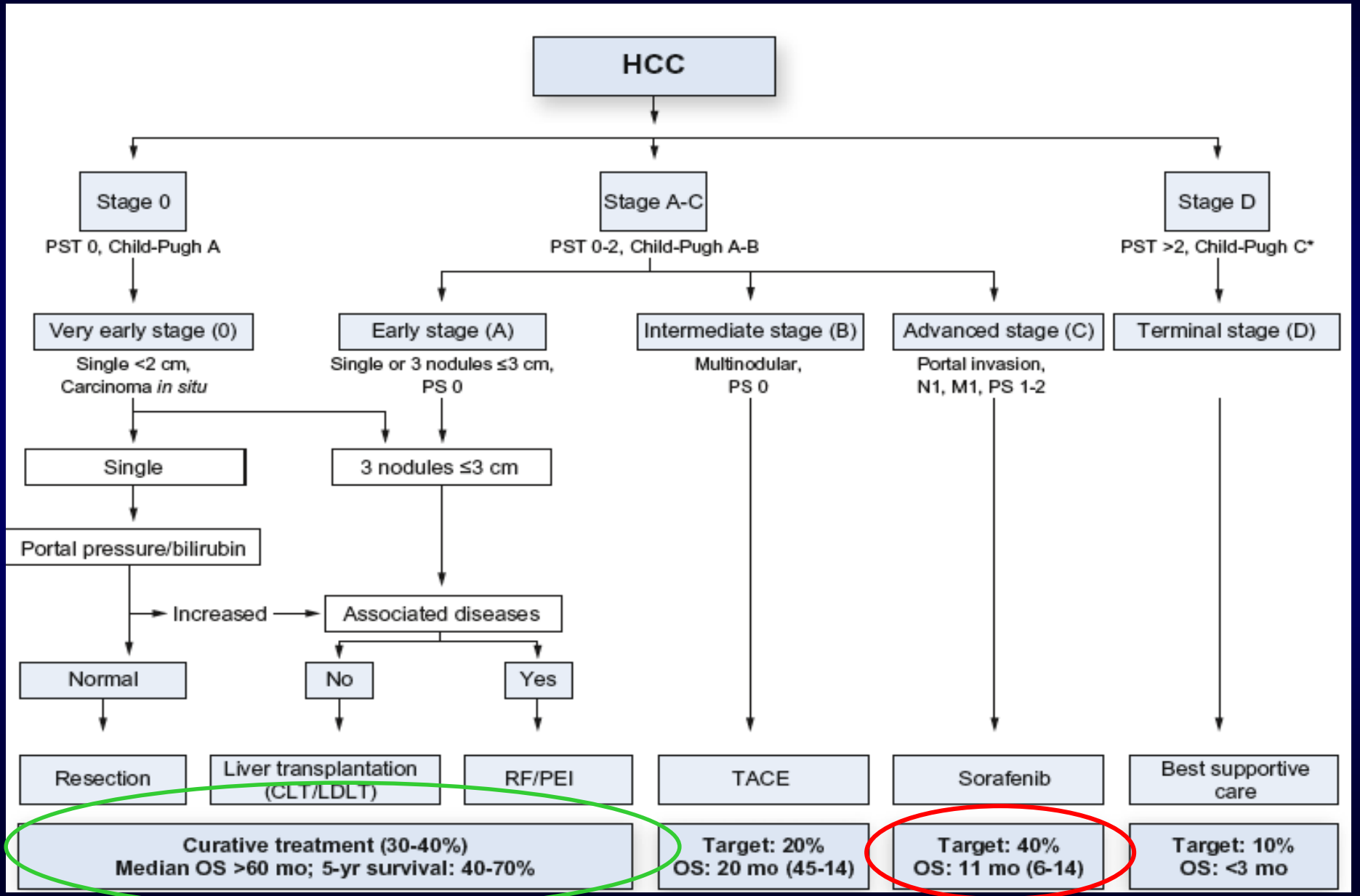
# HCC Progression

**Chronic Liver Disease** → **Cirrhosis** → **HCC**

Nat Genet. 2008;31:339-46.

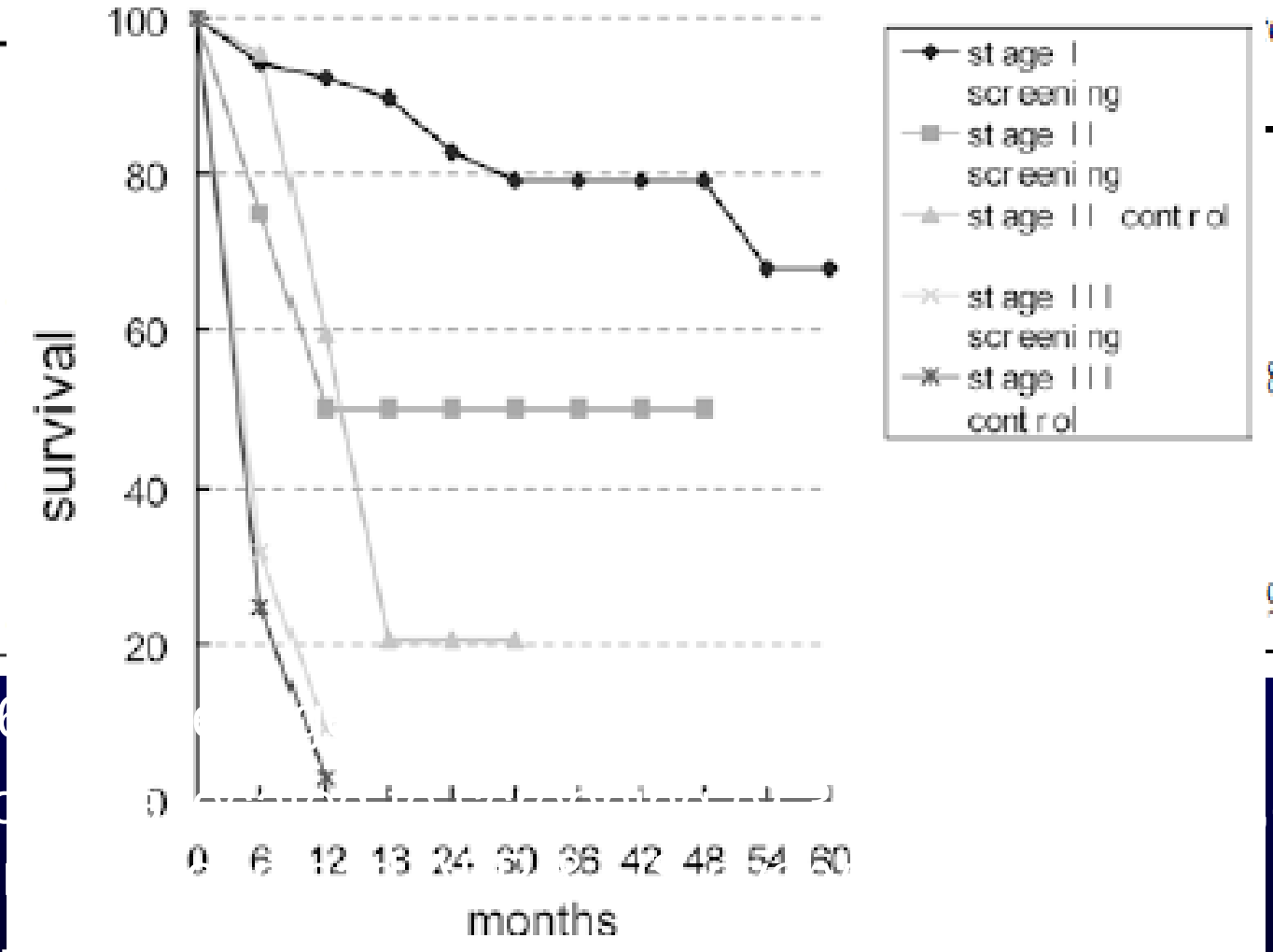
# Treatment allocation



# Surveillance

# Randomized controlled trial of screening for hepatocellular carcinoma

| | oup | Control group |
|---|---|---|
| Stage[a] | | |
| Stage I | | 41,077 |
| Stage II | | 67 |
| Stage III | | 163.1 |
| Small HCC | 89) | |
| Treatment | | |
| Resection | | 54 |
| TACE/PEI | | 131.5 |
| Conservative treatment | 98) | |
| Survival (%)[b] | | |
| 1-year | | |
| 2-year | | |
| 3-year | | |
| 4-year | | |
| 5-year | | |

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- Rando 443).
  Scree
- The pr

Zhang BH J Cancer Res Clin Oncol 2004

# Tumor markers for diagnosis

| Tumor Marker | Sensitivity (%) | Specificity (%) |
|---|---|---|
| α-Fetoprotein (AFP)[15–18] | | |
| >20 ng/mL | 41–65 | 80–94 |
| >200 ng/mL | 20–45 | 99–100 |
| >400 ng/mL | <20 | 99–100 |
| *Lens culinaris* agglutinin-reactive α-fetoprotein (AFP-L3)[24–27,a] | 39–75 | 83–90 |
| Des-γ-carboxyprothrombin (DCP)[29–31,b] | 41–74 | 70–100 |
| Glypican-3 (GPC-3)[36–39] | 40–53 | 90–100 |
| Proteomic profiling[40–43] | 61–92 | 76–91 |

# α-Fetoprotein (AFP)

# Alpha feto protein (α-FP)

- Oncofetal antigen
- Abundant serum protein normally synthesized by the fetal liver
- Re-expressed in certain types of tumors

# Alpha-fetoprotein Prospective Cohort Studies

| Author | No. of cirrhotics | No. of HCC | PPV % | NPV % | Sensitivity % | Specificity % |
|---|---|---|---|---|---|---|
| Pateron | 118 | 14 | 33 | - | 50 | 86 |
| Oka | 260 | 55 | 32 | 82 | 39 | 76 |
| Bolondi | 313 | 61 | 46 | 85 | 41 | 82 |
| Tong | 602 | 31 | 12 | 99 | 41 | 95 |
| Chalasani | 285 | 27 | 30 | - | 63 | 87 |

Marrero JA. Clin Liver Dis 2005;9:235.

# Surveillance guidelines

## EASL-EORTC

- Patients at high risk for developing HCC should be entered into surveillance programs. Groups at high risk are depicted in Table 3
**(evidence 1B/3A; recommendation 1A/B)**

- Surveillance should be performed by experienced personnel in all at-risk populations using abdominal ultrasound every 6 months
**(evidence 2D; recommendation 1B)**

Llovet JM et al 2011

## AASLD

*1. Patients at high risk for developing HCC should be entered into surveillance programs (Level I). The at-risk groups for whom surveillance is recommended are identified in Table 3.*

*3. Surveillance for HCC should be performed using ultrasonography (level II).*

*4. Patients should be screened at 6 month intervals (level II).*

*5. The surveillance interval does not need to be shortened for patients at higher risk of HCC (level III).*

Bruix & Sherman 2010

# Recommendations

"Analysis of recent studies show that alpha-fetoprotein determination lacks adequate sensitivity and specificity for effective surveillance (and for diagnosis)"

Sherman M et al Hepatology 2010

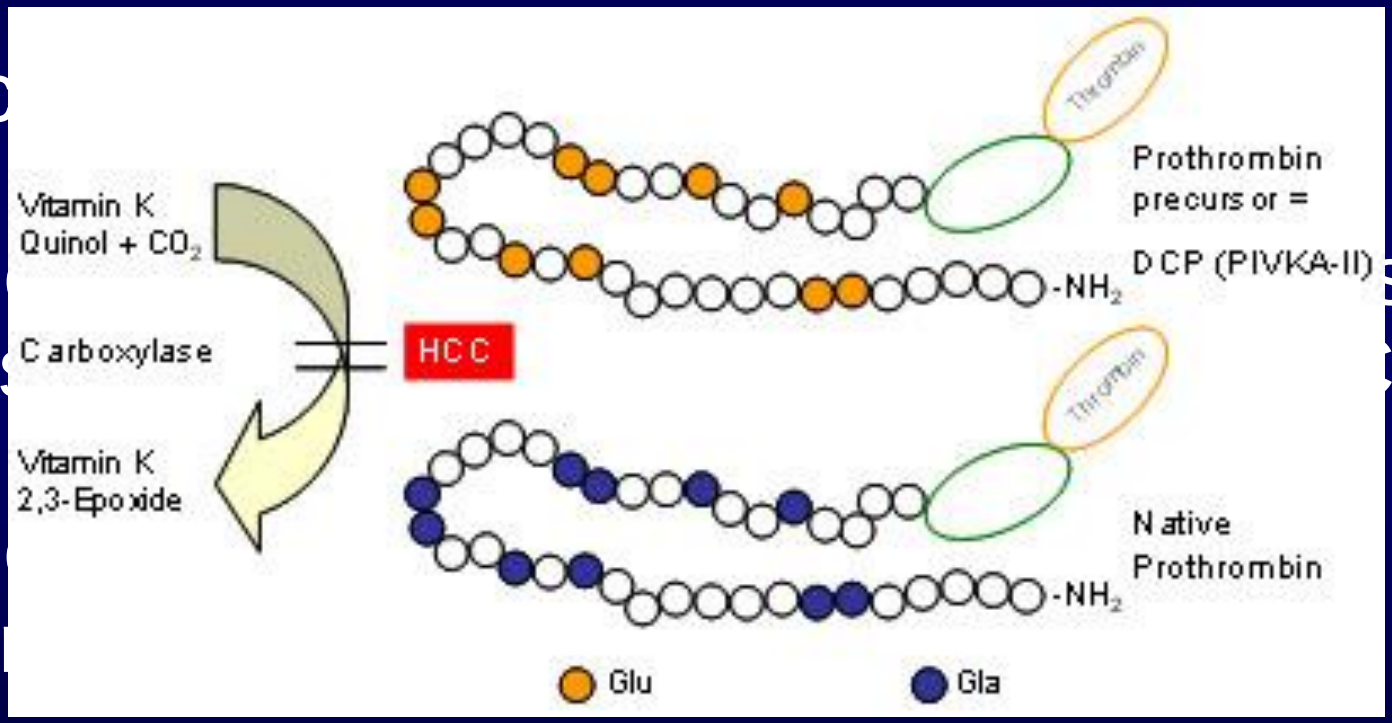
"Accurate tumor biomarkers for early detection need to be developed. Data available with tested biomarkers (i.e. AFP, AFP-L3 and DCP) show that these tests are suboptimal for routine clinical practice **(evidence 2D; recommendation 2B)"**

Llovet JM et al 2011

Gonzalez SA et al. Clin Liver Dis 2012

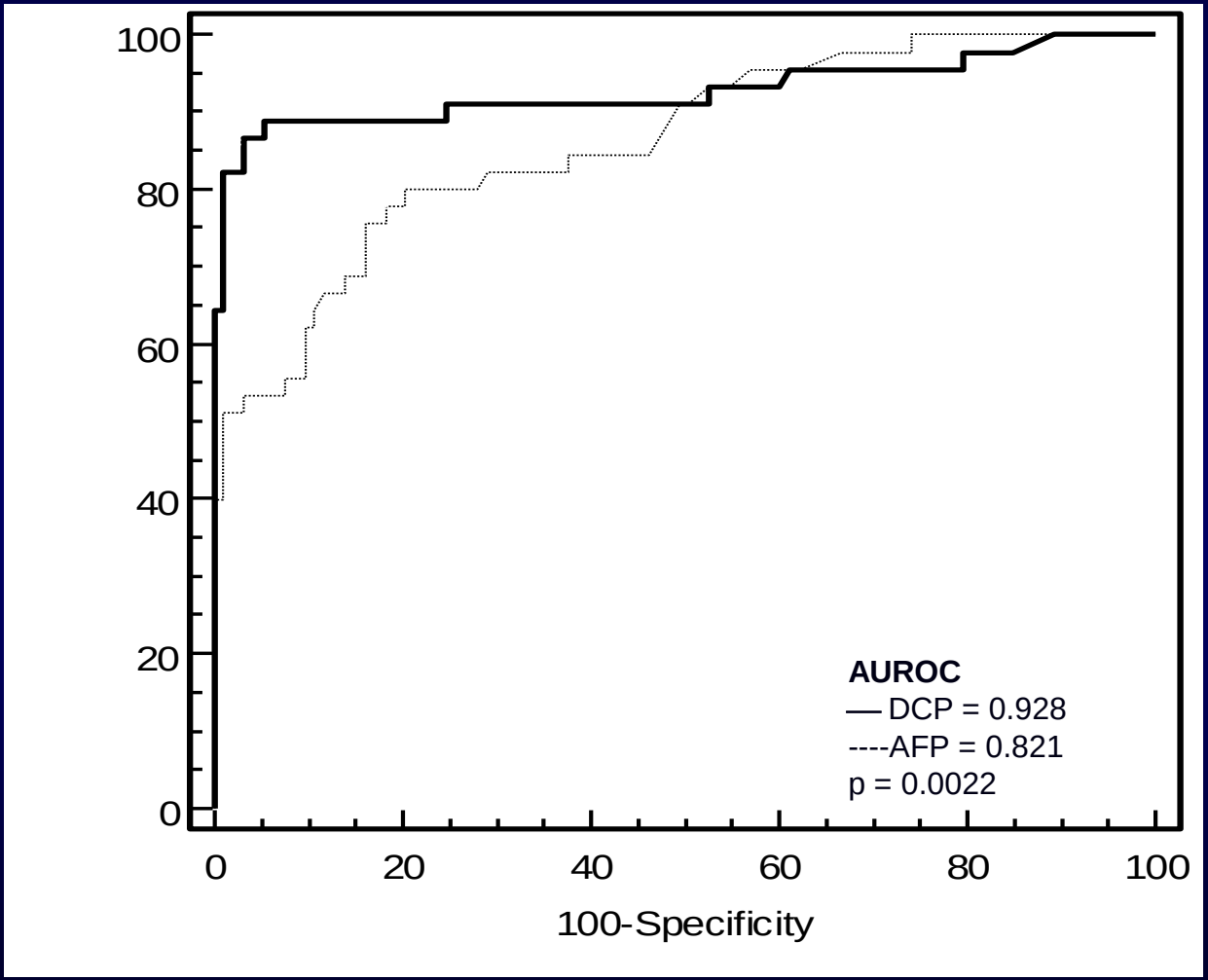
# Des-gamma carboxyprothrombin (DCP) in HCC

- Inc
- Th se has CC
- Th n na




Tsai et al Hepatology 1990;11:481

# DCP Differentiates Cirrhosis from HCC




<u>* Cutoff Values</u>

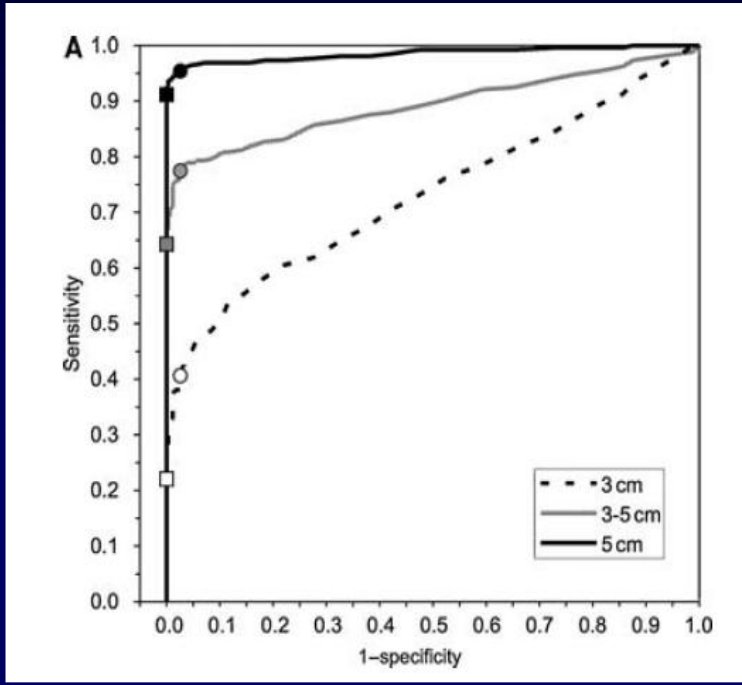
DCP = 150 mAU/ml
- Sens: 89%
- Spec: 96%
- PPV: 91%
- NPV: 88%

AFP = 13 ng/ml
- Sens: 62%
- Spec: 76%
- PPV: 78%
- NPV: 71%

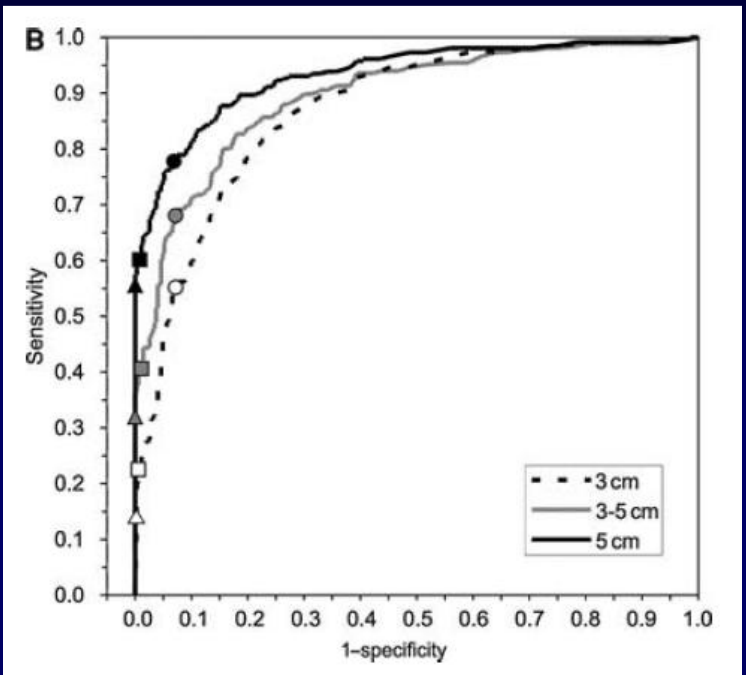
Marrero et al; Hepatology 2003;37:490

# DCP vs. AFP

DCP




AFP

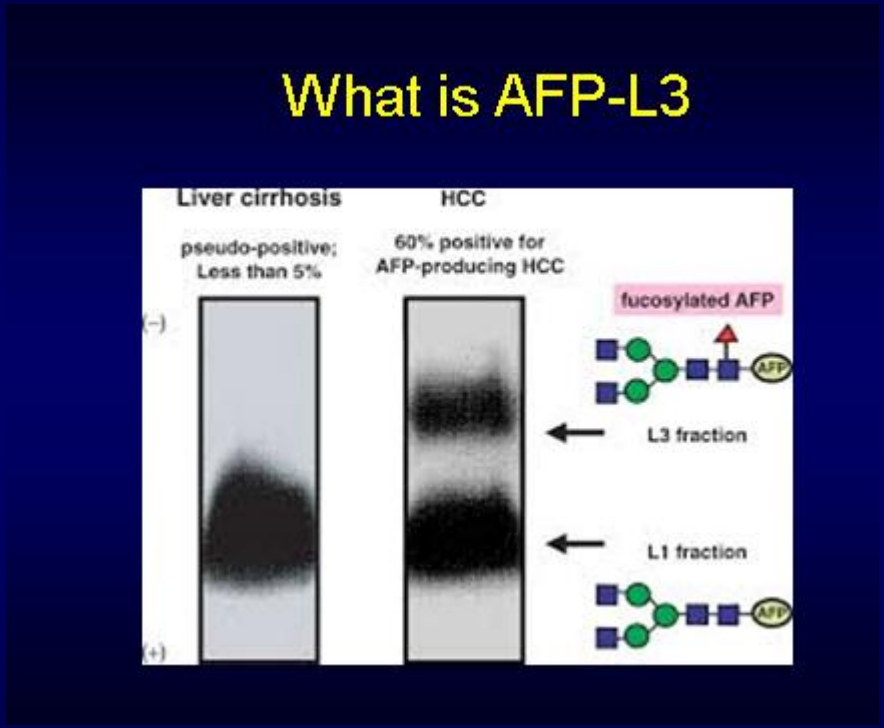



| | DCP (mAU/mL) | | AFP (ng/mL) | | | DCP AFP | |
|---|---|---|---|---|---|---|---|
| Cut-off values | 40 | 100 | 20 | 100 | 200 | 40 | 20 |
| Sensitivities (%) | | | | | | | |
| All tumors | 58 | 44 | 62 | 33 | 26 | 82 | |
| Tumor diameter: | | | | | | | |
| <3 cm | 41 | 22 | 55 | 23 | 14 | 72 | |
| 3–5 cm | 77 | 64 | 68 | 41 | 32 | 93 | |
| >5 cm | 95 | 91 | 78 | 60 | 56 | 99 | |
| Specificities (%) | 97 | 100 | 93 | 99 | 100 | 91 | |

Nakamura S et al AJG 2007

# Lectin-bound Alpha-fetoprotein AFP-L3

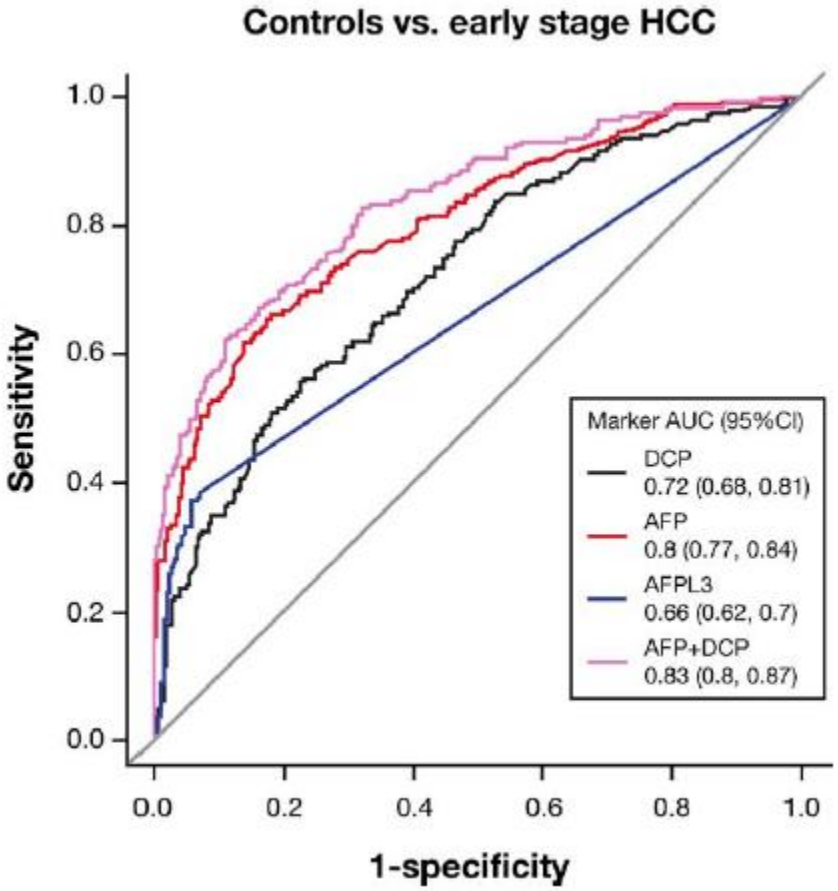
- The sugar chain structures of AFP obtained from patients with LC and HCC have different affinities for lectins
- One subspecies, *Lens culinaris* agglutinin (LCA)-reactive AFP (AFP-L3) is more specific to HCC




Yamagata et al. Clin Chim Acta. 2003;327:59

Combinations?

# DCP, AFP-L3 & AFP in combination only marginally improve detection of early HCC




| Marker | Cutoff | Sensitivity, % (95% CI) | Specificity, % (95% CI) |
|---|---|---|---|
| All HCC (n = 419) | | | |
| AFP | 20 | 59 (55–64) | 90 (86–93) |
| DCP | 150 | 74 (70–79) | 70 (65–74) |
| AFP-L3% | 10 | 42 (37–47) | 97 (93–100) |
| AFP + DCP | AFP = 20 or DCP = 150 | 86 (82–89) | 63 (58–67) |
| Early stage HCC (n = 208)[a] | | | |
| AFP | 20 | 53 (46–59) | 90 (87–93) |
| DCP | 150 | 61 (55–68) | 70 (65–74) |
| AFP-L3% | 10 | 28 (22–34) | 97 (93–100) |
| AFP + DCP | AFP = 20 or DCP = 150 | 78 (72–83) | 62 (58–67) |

Marrero JA et al Gastroenterology 2009

# Performance Characteristics of Markers-Early Stage (n=52)

| Marker | AUROC | Sens | Spec | +LR | -LR |
|---|---|---|---|---|---|
| AFP 14 ng/mL | 0.81 | 64 | 88 | 8.5 | 0.38 |
| AFP-L3 3% | 0.71 | 50 | 88 | 4.5 | 0.56 |
| DCP 150 mAU/ml | 0.93 | 92 | 93 | 13.9 | 0.08 |
| Comb | 0.94 | 90 | 91 | 10.7 | 0.11 |

Sterling RK et al CGH 2009

# DCP, AFP-L3 and AFP in combination only marginally improve detection of HCC

| Analyte cut-off value | AFP-L3% | | | | DCP | | | | AFP | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 10% | | | | *ng/mL* | | | | | |
| AFP range: *ng/mL* | <20 | 20–199.9 | ≥200 | All range | <20 | 20–199.9 | ≥200 | All range | 20 ng/mL | 200 ng/mL |
| In all patients (G1, G2, and G3) | | | | | | | | | | |
| Total number (HCC number) | 241 (29) | 111 (29) | 20 (16) | 372 (74) | 241 (29) | 111 (29) | 20 (16) | 372 (74) | 372 (74) | 372 (74) |
| Sensitivity | 20.7% | 37.9% | 62.5% | 36.5% | 24.1% | 44.8% | 56.3% | 39.2% | 60.8% | 21.6% |
| Specificity | 93.4% | 86.6% | 100.0% | 91.6% | 89.2% | 90.2% | 100.0% | 89.6% | 71.1% | 98.7% |
| PPV | 30.0% | 50.0% | 100.0% | 51.9% | 23.3% | 61.9% | 100.0% | 48.3% | 34.4% | 80.0% |
| NPV | 89.6% | 79.8% | 40.0% | 85.3% | 89.6% | 82.2% | 36.4% | 85.6% | 88.0% | 83.5% |
| In G2 and G3 | | | | | | | | | | |
| Total number (HCC number) | 228 (16) | 95 (13) | 9 (5) | 332 (34) | 228 (16) | 95 (13) | 9 (5) | 332 (34) | 332 (34) | 332 (34) |
| Sensitivity | 31.3% | 53.8% | 60.0% | 44.1% | 18.8% | 38.5% | 60.0% | 32.4% | 52.9% | 14.7% |
| Specificity | 93.4% | 86.6% | 100.0% | 91.6% | 89.2% | 90.2% | 100.0% | 89.6% | 71.1% | 98.7% |
| PPV | 26.3% | 38.9% | 100.0% | 37.5% | 11.5% | 38.5% | 100.0% | 26.2% | 17.3% | 55.6% |
| NPV | 94.7% | 92.2% | 66.7% | 93.5% | 93.6% | 90.2% | 66.7% | 92.1% | 93.0% | 91.0% |

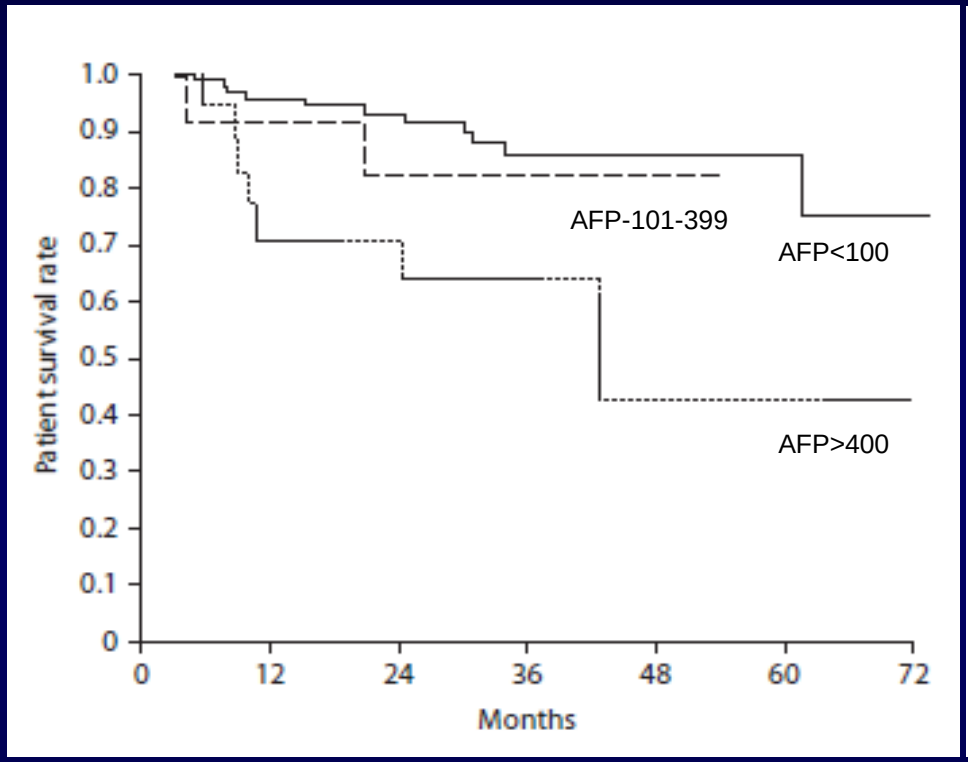
| | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|
| In all patients (G1, G2, and G3) | | | | |
| AFP alone, ≥20 ng/mL | 60.8% | 71.1% | 34.4% | 88.0% |
| AFP-L3% alone, ≥10% | 36.5% | 91.6% | 51.9% | 85.3% |
| DCP alone, ≥7.5 ng/mL | 39.2% | 89.6% | 48.3% | 85.6% |
| AFP + AFP-L3% | 68.9% | 66.4% | 33.8% | 89.6% |
| AFP + DCP | 70.3% | 63.4% | 32.3% | 89.6% |
| AFP-L3% + DCP | 62.2% | 82.6% | 46.9% | 89.8% |
| AFP + AFP-L3% + DCP | 77.0% | 59.4% | 32.0% | 91.2% |

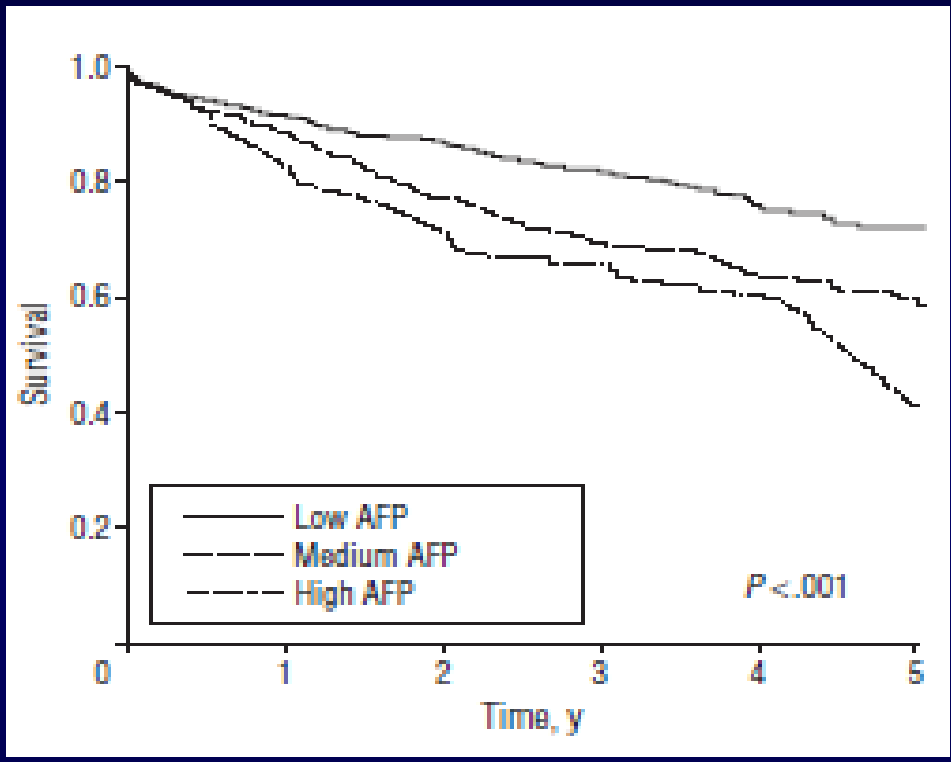
Sterling RK et al CGH 2009

# Tumor markers for other uses

- Transplantation
- Assessment of therapy

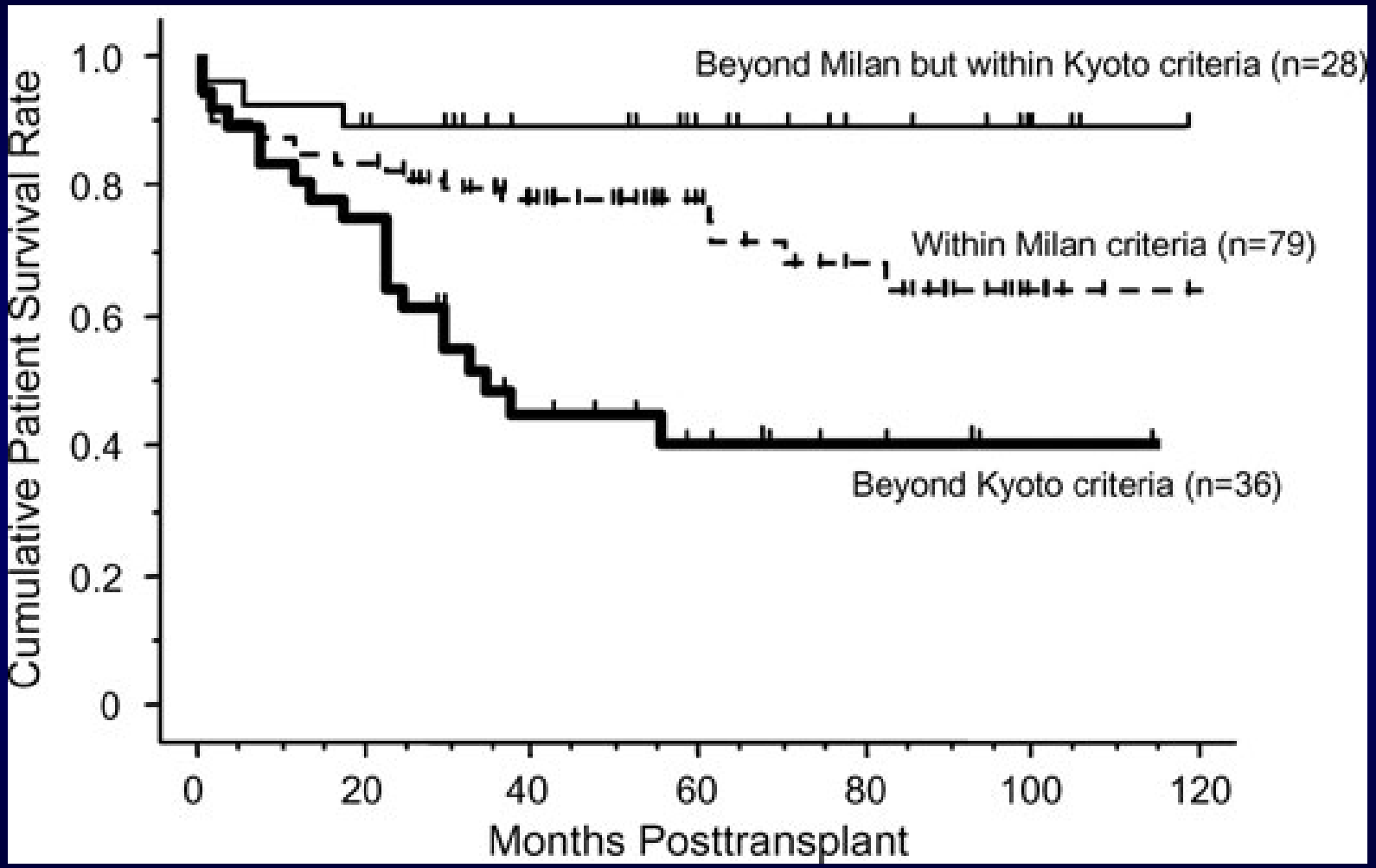
# AFP Levels Impact on post OLT Survival




**Kwon CHD et al. Dig Dis 2007,**
**Mailey D et al Arch Surg 2011**

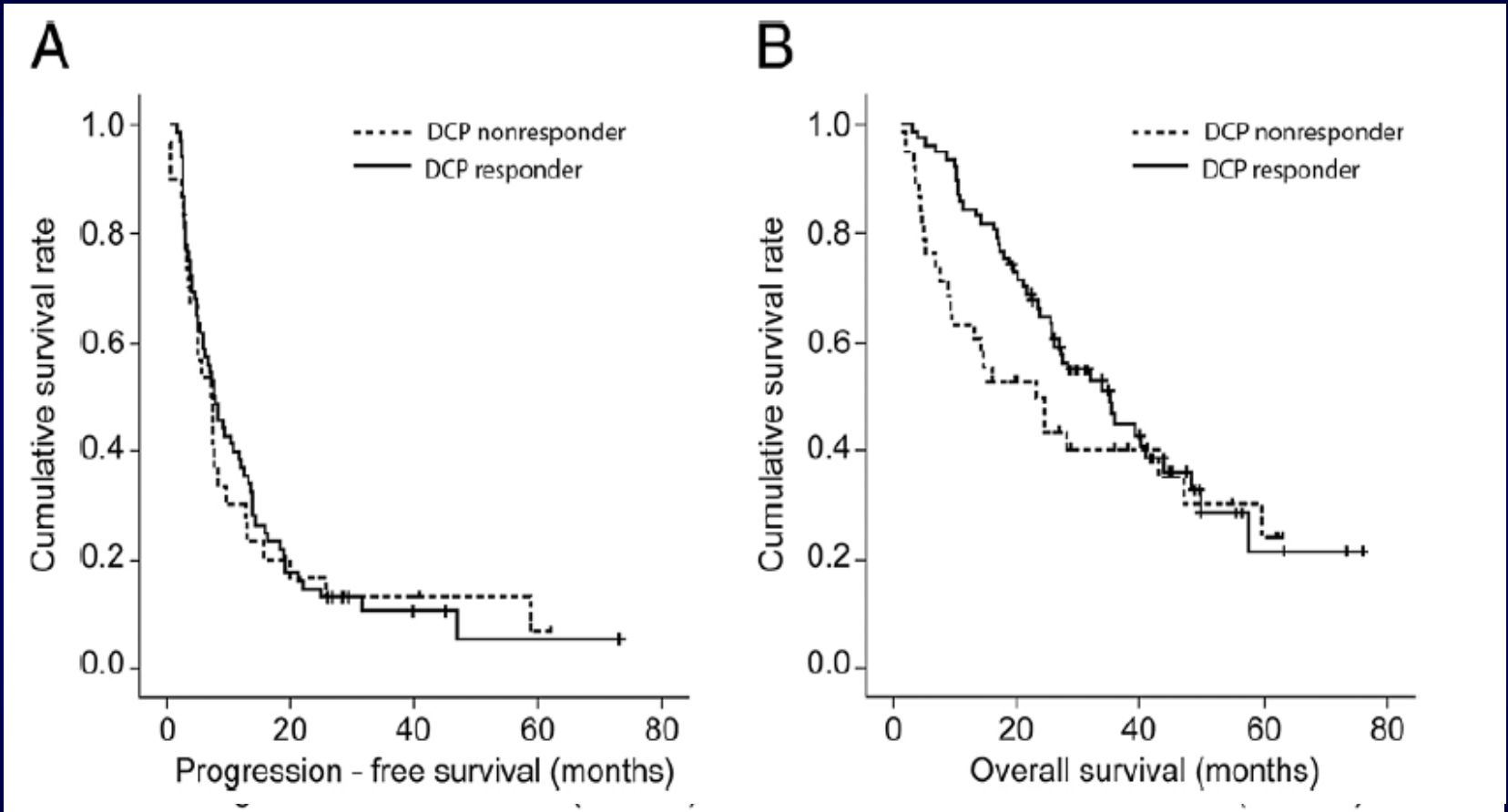
# des-gamma-carboxy prothrombin Levels Impact on OLT Survival




*Tumor size ≤ 5 cm, ≤10 nodules (5-10 rule) and DCP ≤400 mAU/mL*

**Fujiki M, et al. Am J Transplant 2009**

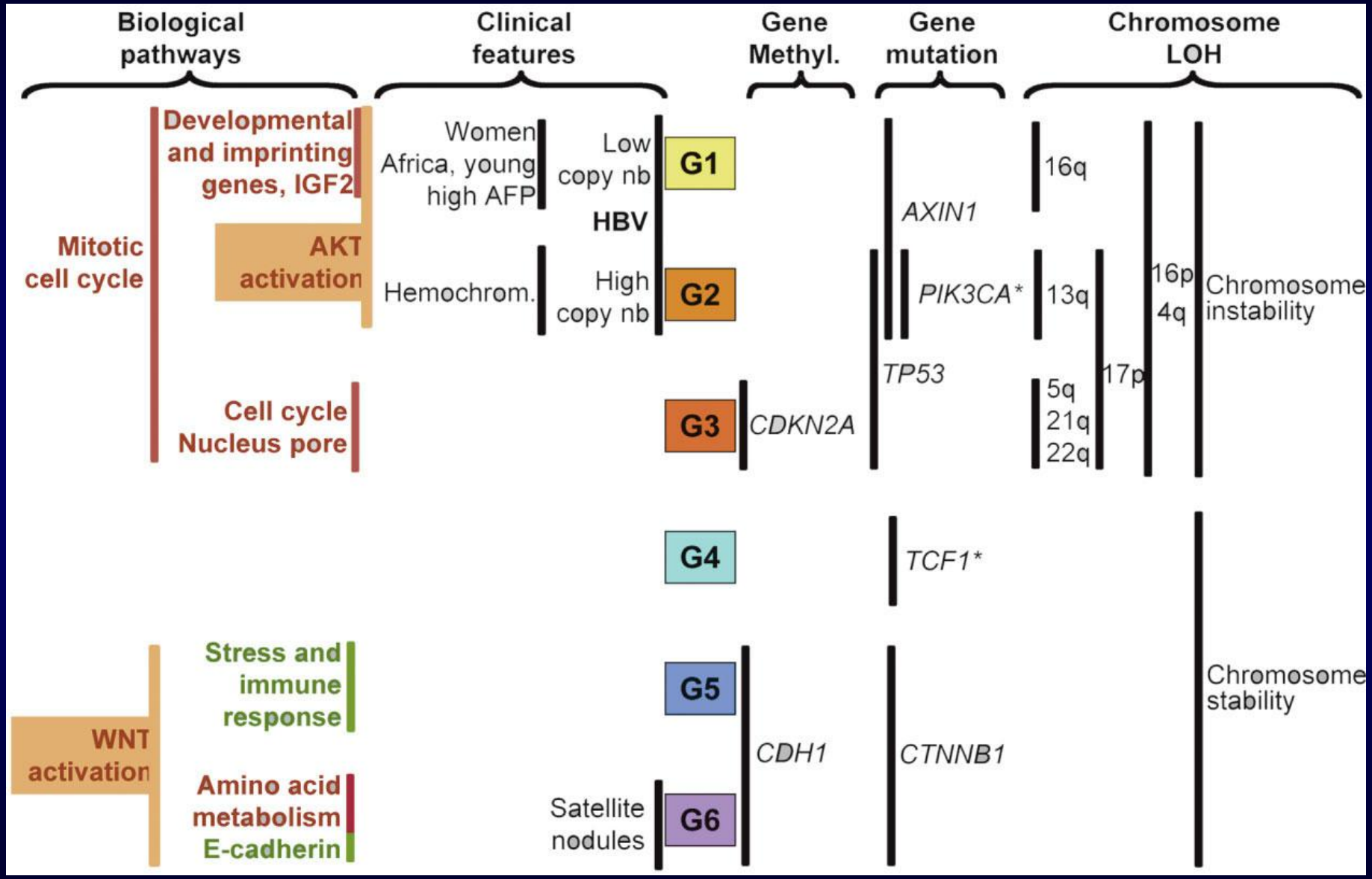
# AFP but not DCP response predict survival after TACE




Lee YK et al. Cancer 2013

# The future

# Gene profiling

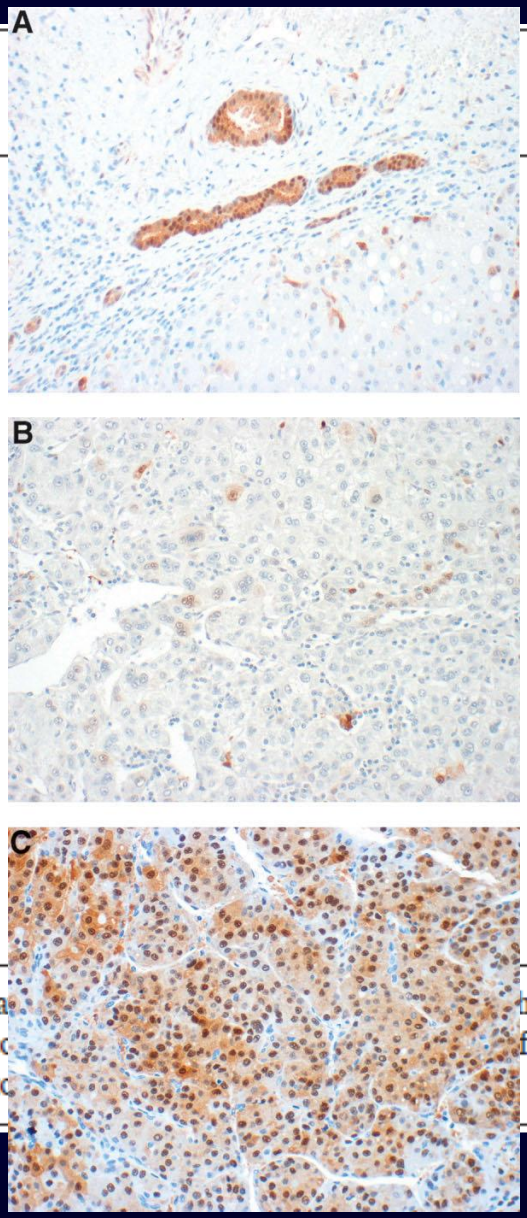


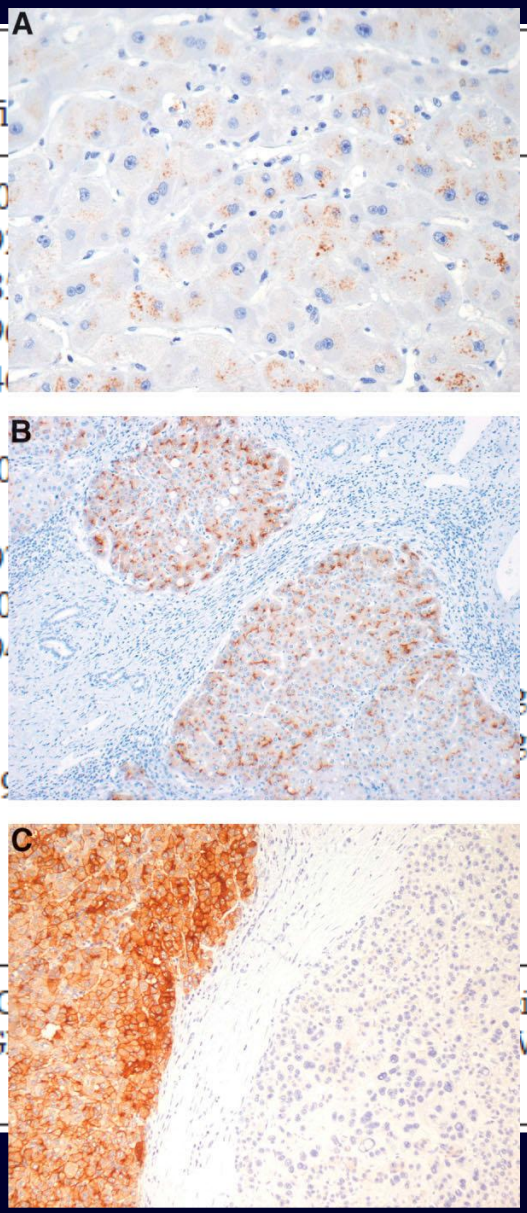

Boyault S et al. Hepatology 2007

# New tumor markers and their uses

| Markers | Sensitivity (%) | Specifi |
|---|---|---|
| AFP | 41.0-65.0 | 80.0 |
| AFP-L3 | 96.9 | 9 |
| HSP70 | 57.5 | 8 |
| GPC3 | 77.0 | 9 |
| SCCA | 84.0 | 4 |
| GP73 | 76.9 | |
| FC-GP73 | 90.0 | 10 |
| GGT | 43.8 | |
| AFU | 90.0 | 9 |
| AFU+AFP | 95.0 | 10 |
| TGF-β1 | 89.5 | 9 |
| VEGF | - | |
| AFP-mRNA | - | |
| miR-21 | 87.3 | |
| miR-500 | - | |
| miR-29 | - | |
| miR-122 | - | |

HCC, hepatocellular ca… heat shock proteins 70; GPC3, … inoma antigen; FC-GP73, fuc… ferase; AFU, α-l-fucosidase; TG… VEGF, endothelial growth fact…




Zhu K et al. Biomarker Res 2014

# Summary

- HCC is the only major cancer who's incidence is increasing
- Currently only a minority of HCC patients are diagnosed at the curative stage.
- Tested biomarkers (i.e. AFP, AFP-L3 and DCP) are suboptimal for routine clinical practice
- There is a need to develop accurate tumor biomarkers for early detection, prognosis and tx assessment.

Tel-Aviv Sourasky Medical Center

# Thank You For Your Attention

# פרופ' אורן שבולת

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