Hepatocellular Carcinoma: The New Frontier

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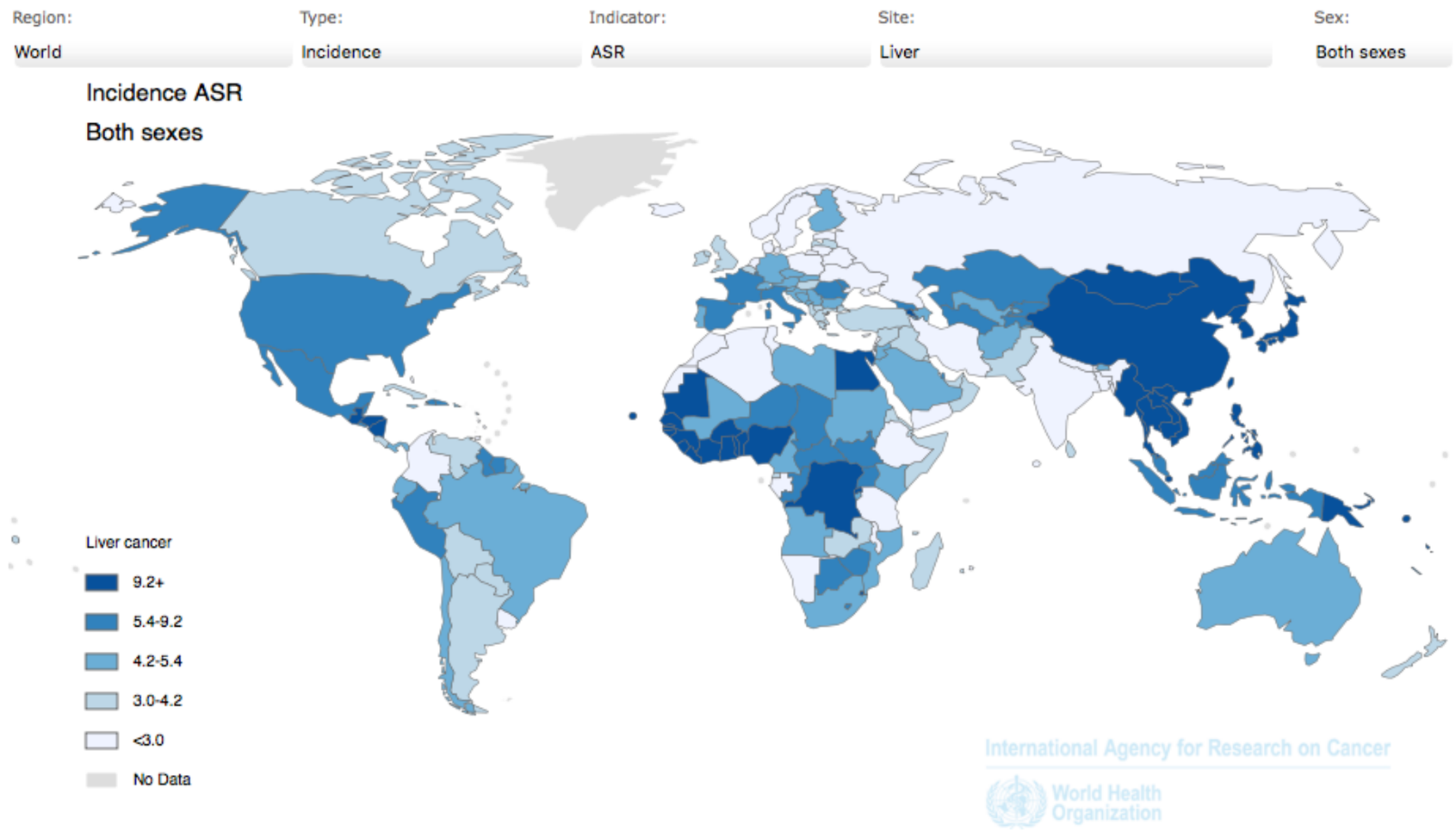
Outline

- Epidemiology
- HCC and chronic viral hepatitis: direct or indirect carcinogenesis?
- The new frontier: HCC -omics

Epidemiology of HCC

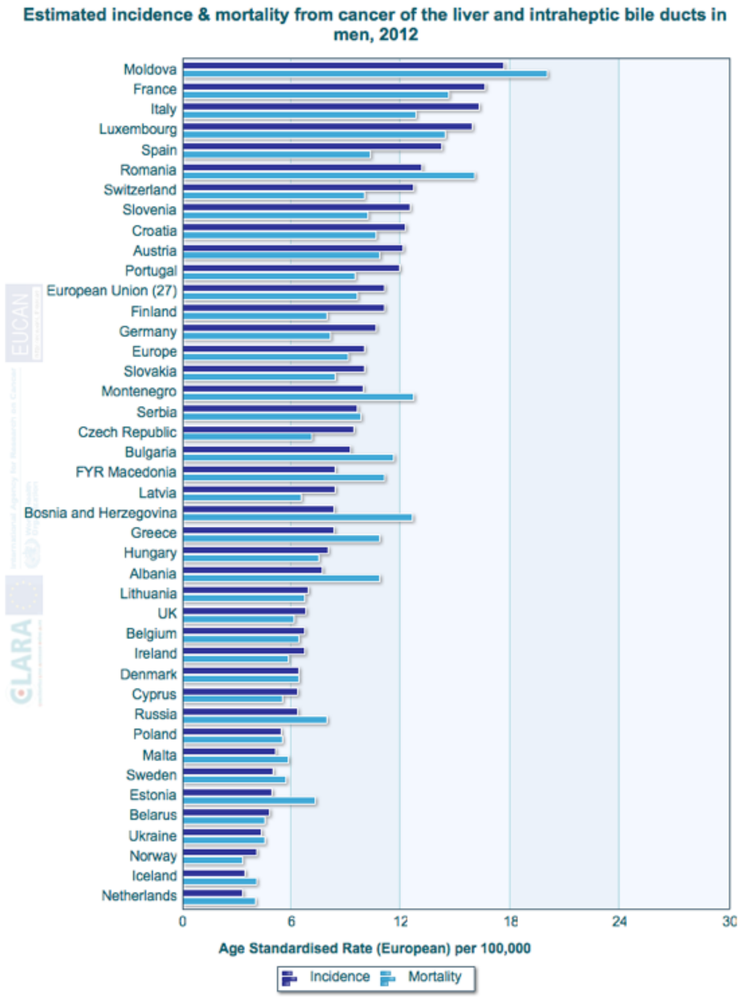
- Worldwide, liver cancer is the sixth most common cancer (749’000 new cases), the third cause of cancer-related death (692’000), and accounts for 7% of all cancers
- 90% of liver cancers are HCCs
- 80%-90% of HCCs arise in cirrhotic livers, > 95% of HCC develop on the background of chronic liver disease
- Incidence of HCC increases with age, reaching a peak at 70 years (in Chinese and black African populations, mean age is younger)
- Male to female ratio = 2.4

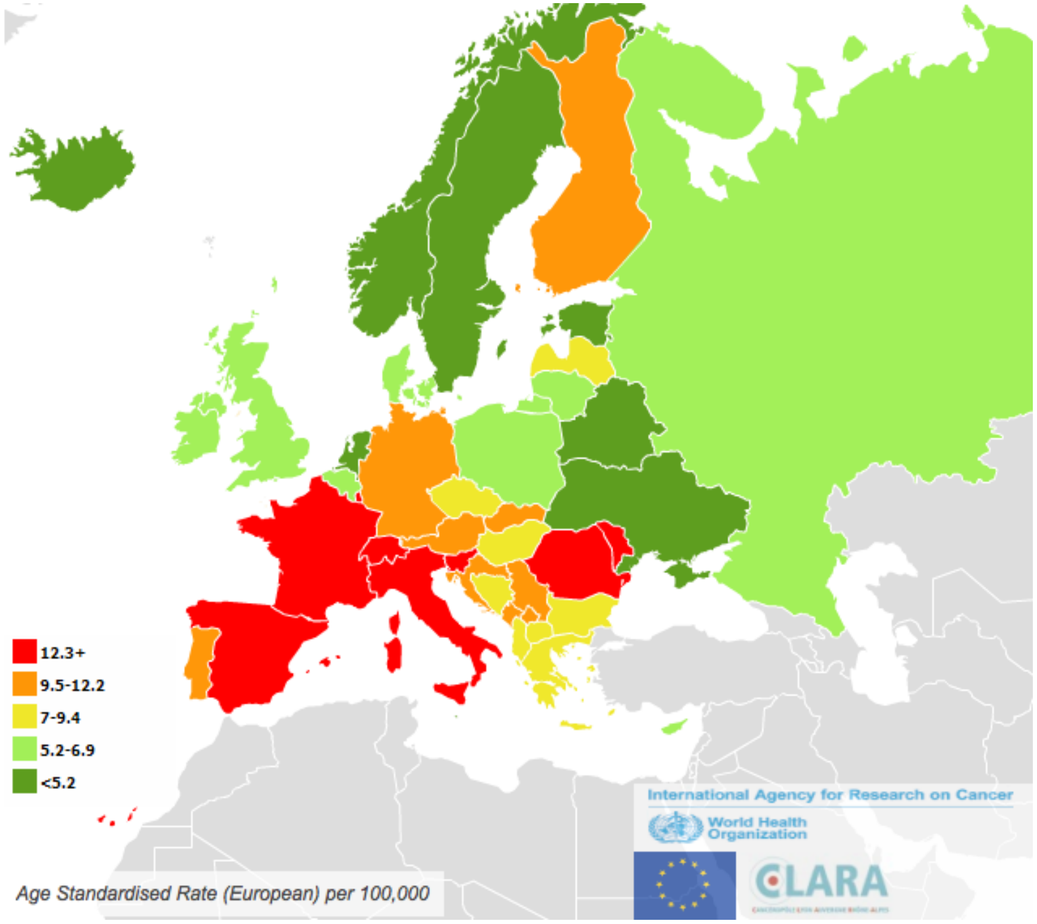
Global HCC incidence



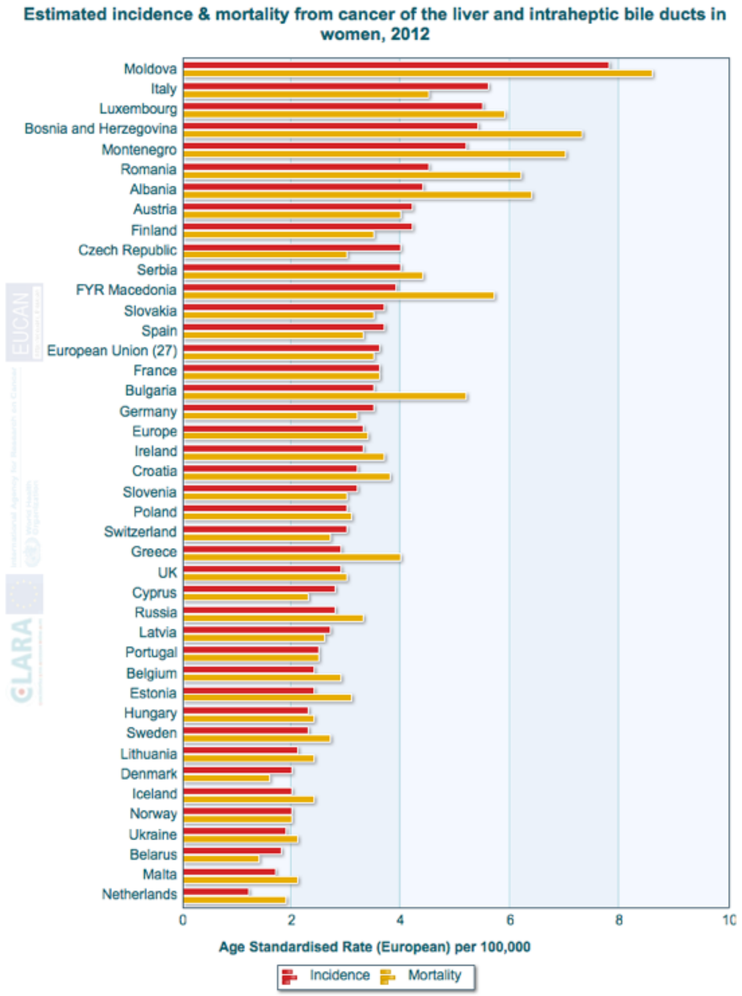
Source: GLOBOCAN 2012 (IARC)

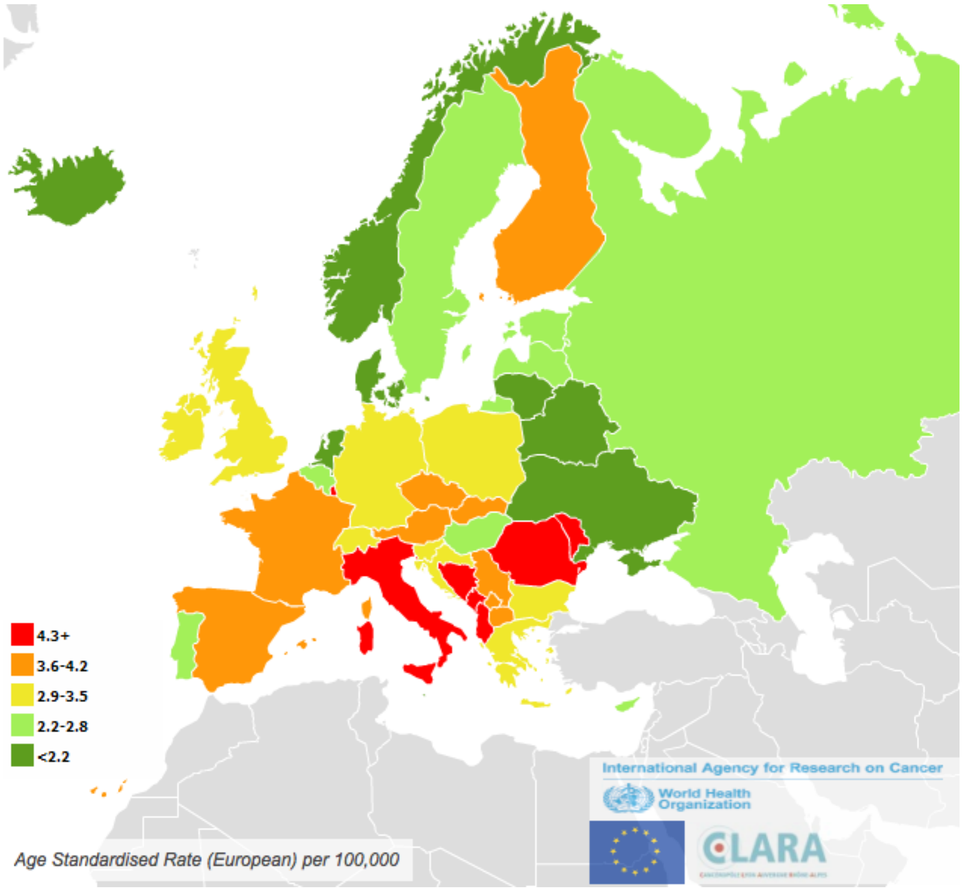
HCC incidence Europe: Men



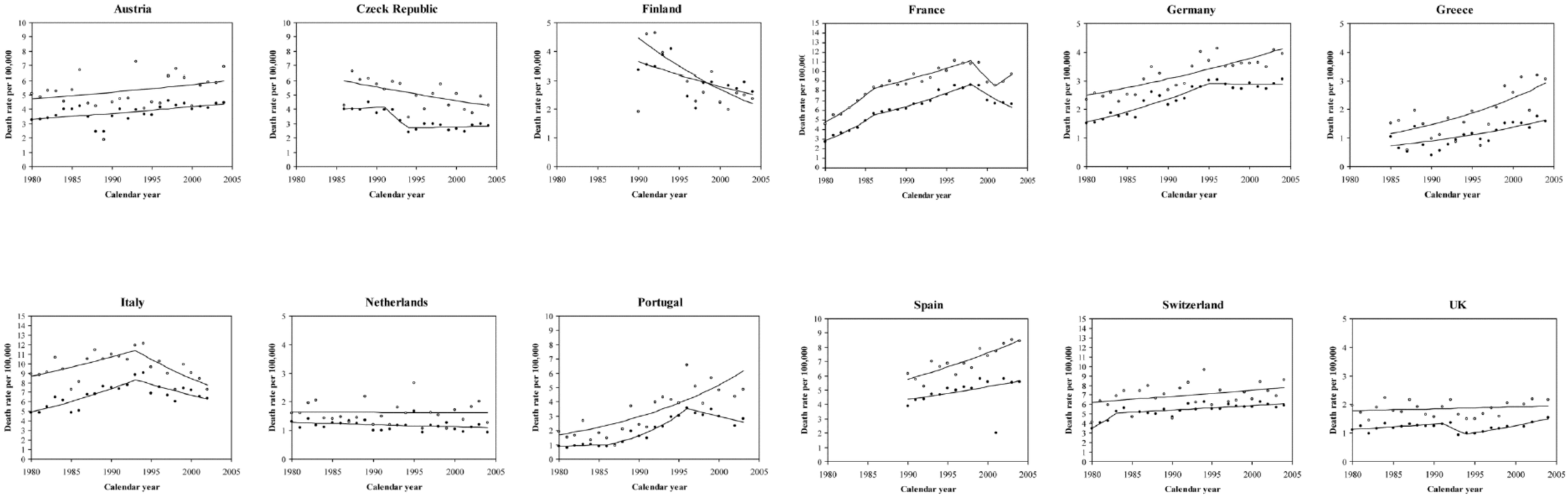


HCC incidence Europe: Women





Trends in HCC incidence in Europe



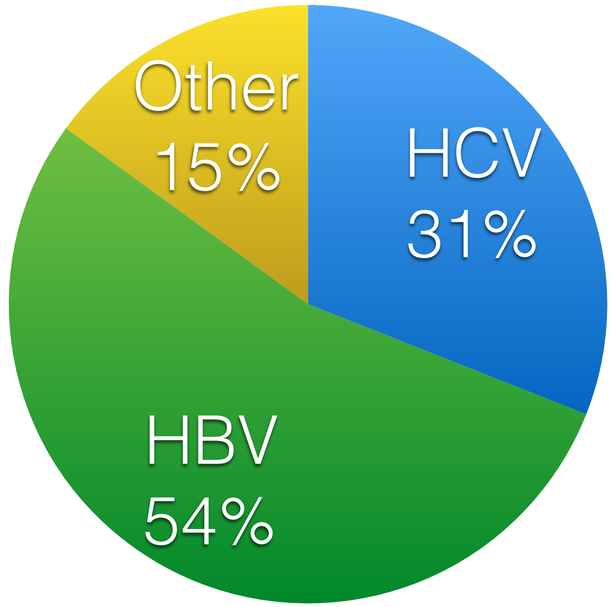
Bosetti et al, Hepatology, 2008

HCC risk factors

Table 2. Geographical distribution of main risk factors for HCC worldwide.*

Geographic area	AAIR	Risk factors		Alcohol	Others
	M/F	HCV (%)	HBV (%)	(%)	(%)
Europe	6.7/2.3	60-70	10-15	20	10
Southern	10.5/3.3				
Northern	4.1/1.8				
North America	6.8/2.3	50-60	20	20	10 (NASH)
Asia and Africa		20	70	10	10 (Aflatoxin)
Asia	21.6/8.2				
China	23/9.6				
Japan	20.5/7.8	70	10-20	10	10
Africa	1.6/5.3				
WORLD	16/6	31	54	15	

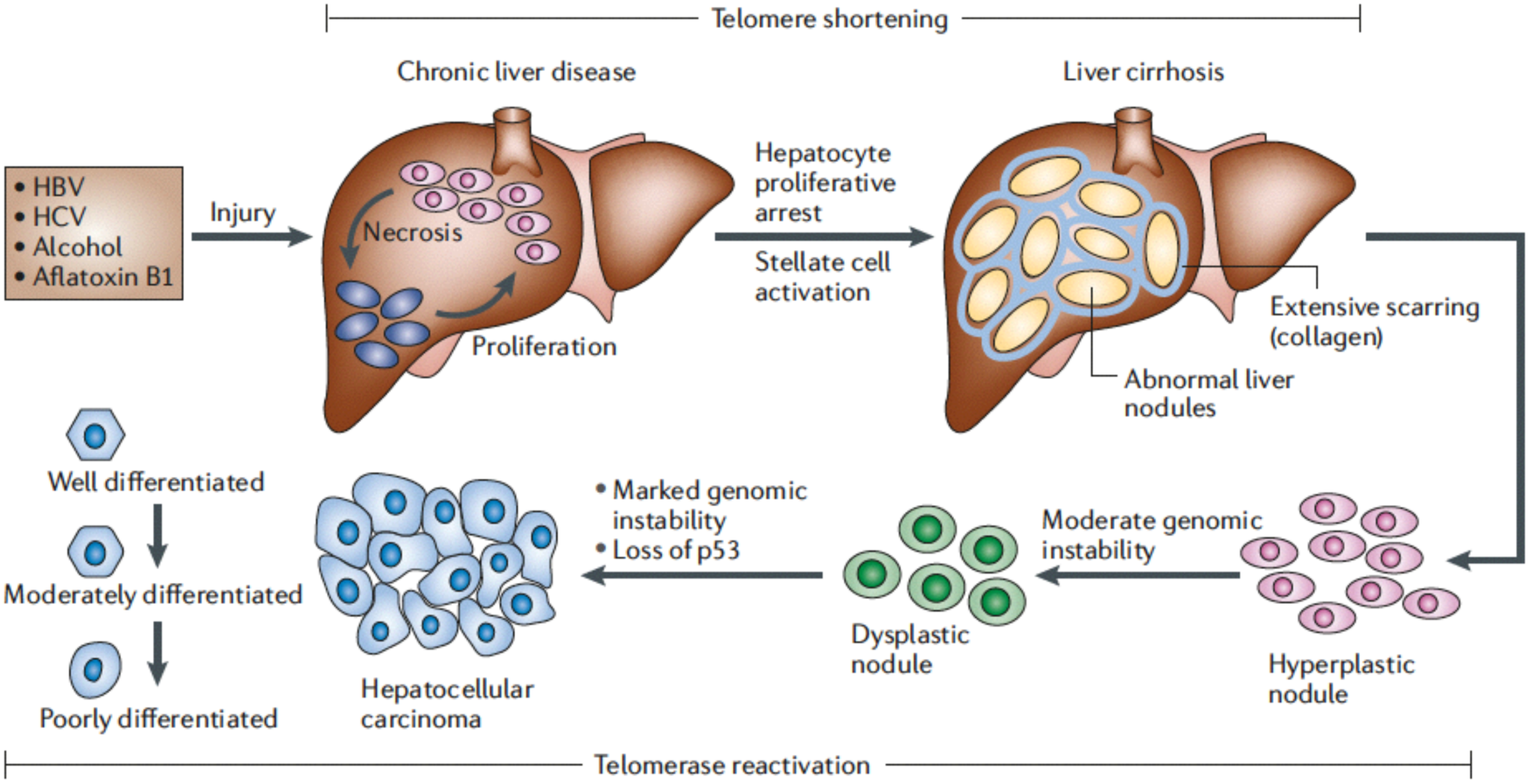
*Updated from Llovet *et al.* [99], according to IARC data [4]. AAIR, age-adjusted incidence rate.



World

EASL-EORTC clinical practice guidelines HCC, J Hepatol 2012

Histopathological progression



Farazi and DePinho, Nat Rev Cancer, 2006

Chronic viral hepatitis and HCC: direct versus indirect carcinogenesis

Direct

- Viruses induce oxidative stress and DNA damage in infected liver cells
- Viruses deregulate cell cycle checkpoints of host cells
- Oncogenic mutations are fixed and propagated to daughter cells

Indirect

- The immune response to chronic viral infection results in liver inflammation
- Cytokines causes oxidative stress and apoptosis in uninfected and infected cells
- Increased hepatocyte proliferation in response to apoptosis enhances the chances that oncogenic mutations are fixed and propagated to daughter cells

HBV and HCC

HEPATOCELLULAR CARCINOMA AND HEPATITIS B VIRUS

A Prospective Study of 22 707 Men in Taiwan

R. PALMER BEASLEY LU-YU HWANG
CHIA-CHIN LIN CHIA-SIANG CHIEN

University of Washington Medical Research Unit, Taipei; Institute of Public Health, College of Medicine, National Taiwan University; and Government Employees' Clinic Centre, Taipei, Taiwan

Summary A prospective general population study of 22 707 Chinese men in Taiwan has shown that the incidence of primary hepatocellular carcinoma (PHC) among carriers of hepatitis B surface antigen (HBsAg) is much higher than among non-carriers (1158/100 000 *vs* 5/100 000 during 75 000 man-years of follow-up). The relative risk is 223. PHC and cirrhosis accounted for 54·3% of the 105 deaths among HBsAg carriers but accounted for only 1·5% of the 202 deaths among non-carriers. These findings support the hypothesis that hepatitis B virus has a primary role in the aetiology of PHC.

Beasley et al, Lancet, 1981

- 22'707 Chinese men in Taiwan
- 3454 HBsAg positive (15.2%)
  19253 HBsAg negative (84.8%)
- mean follow-up 3.3 years
  (75'000 man-years)
- 41 men died of HCC
  40 of them were HBsAg positive
- relative risk 223

HBV viral load and HCC

- prospective cohort study of 3’653 participants (30-65 y) positive for HBsAg recruited in Taiwan between 1991 and 1992
- mean follow-up 11.4 years (41’779 person-years)
- treatment was not reimbursed in Taiwan until 2003: participants did nor receive antiviral treatment *(natural history cohort)*
- 164 incident cases of HCC

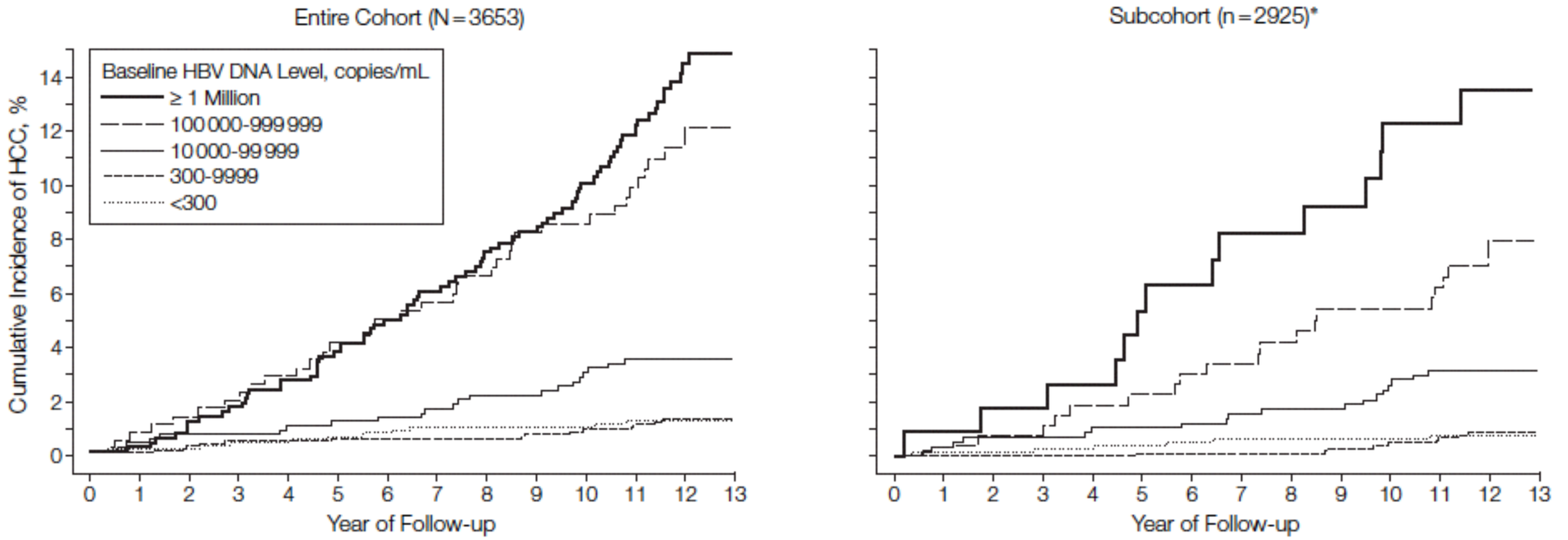
Table 1. Baseline Characteristics of the Study Cohort

	No. (%) of Participants (N = 3653)*
Sex	
Female	1393 (38)
Male	2260 (62)
Age, y	
30-39	1216 (33)
40-49	1014 (28)
50-59	1058 (29)
≥60	365 (10)
Cigarette smoking†	
No	2416 (66)
Yes	1234 (34)
Alcohol consumption‡	
No	3195 (87)
Yes	451 (12)
Hepatitis B e antigen	
Seronegative	3088 (85)
Seropositive	565 (15)
Level of ALT, U/L	
<45	3435 (94)
≥45	218 (6)
Liver cirrhosis§	
No	3584 (98)
Yes	69 (2)

Abbreviations: ALT, alanine aminotransferase; HBV, hepatitis B virus.

Chen et al, JAMA, 2006

Figure 2. Cumulative Incidence of Hepatocellular Carcinoma by Serum HBV DNA Level at Study Entry



No. at Risk

Baseline HBV DNA Level, copies/mL														
≥1 Million	627	621	611	604	593	582	571	561	550	541	528	513	499	414
100 000-999 999	349	346	342	338	333	327	321	317	310	304	302	294	288	228
10 000-99 999	643	637	633	633	627	625	622	615	609	606	597	588	586	490
300-9999	1161	1155	1146	1139	1137	1131	1129	1123	1119	1113	1102	1091	1082	879
<300	873	865	862	854	850	845	836	826	823	819	814	807	802	720

116	115	113	113	111	108	105	101	101	100	95	94	92	78
271	271	269	268	265	262	259	256	250	246	246	241	237	186
595	590	586	586	581	580	578	572	568	566	557	548	546	454
1104	1099	1095	1090	1088	1082	1080	1074	1070	1065	1055	1044	1036	847
839	832	830	823	819	815	806	797	794	790	786	780	775	697

All participants were seropositive for the hepatitis B surface antigen (HBsAg) and seronegative for antibodies against the hepatitis C virus. Asterisk indicates these participants were seronegative for the hepatitis B e antigen and had a normal level of serum alanine aminotransferase and did not have liver cirrhosis at study entry. HBV indicates hepatitis B virus; HCC, hepatocellular carcinoma.

Chen et al, JAMA, 2006

Table 3. Risk Factors for Hepatocellular Carcinoma at Study Entry

	No. (%) of Participants (N = 3653)	Person-Years of Follow-up	No. of Hepatocellular Carcinoma Cases	Incidence Rate Per 100 000 Person-Years	Crude HR (95%CI)*	*P* Value
Sex						
Female	1393 (38)	16307	29	178	1.0	
Male	2260 (62)	25472	135	530	3.0 (2.0-4.5)	<.001
Age, y						
30-39	1216 (33)	14393	16	111	1.0	
40-49	1014 (28)	11776	47	399	3.6 (2.0-6.4)	<.001
50-59	1058 (29)	11837	67	566	5.1 (3.0-8.9)	<.001
≥60	365 (10)	3773	34	901	8.3 (4.6-15.0)	<.001
Cigarette smoking†						
No	2416 (66)	28037	90	321	1.0	
Yes	1234 (34)	13704	71	518	1.7 (1.2-2.3)	<.001
Alcohol consumption‡						
No	3195 (87)	36779	121	329	1.0	
Yes	451 (12)	4928	42	852	2.6 (1.8-3.7)	<.001
Hepatitis B e antigen						
Seronegative	3088 (85)	35584	94	264	1.0	
Seropositive	565 (15)	6195	70	1130	4.3 (3.2-5.9)	<.001
Level of ALT, U/L						
<45	3435 (94)	39469	133	337	1.0	
≥45	218 (6)	2310	31	1342	4.1 (2.8-6.0)	<.001
Liver cirrhosis§						
No	3584 (98)	41270	131	317	1.0	
Yes	69 (2)	509	33	6482	21.8 (14.9-32.0)	<.001
Level of HBV DNA, copies/mL						
<300 (Undetectable)	873 (24)	10154	11	108	1.0	
300-9999	1161 (32)	13518	15	111	1.0 (0.5-2.2)	.96
10 000-99 999	643 (18)	7404	22	297	2.7 (1.3-5.6)	.006
100 000-999 999	349 (9)	3845	37	962	8.9 (4.6-17.5)	<.001
≥1 million	627 (17)	6858	79	1152	10.7 (5.7-20.1)	<.001

Abbreviations: ALT, alanine aminotransferase; CI, confidence interval; HBV, hepatitis B virus; HR, hazard ratio.
*Cox proportional hazard models were used.
†Data were not available for 3 participants.
‡Data were not available for 7 participants.
§Diagnosed with ultrasonography within 6 months of study entry.

Chen et al, JAMA, 2006

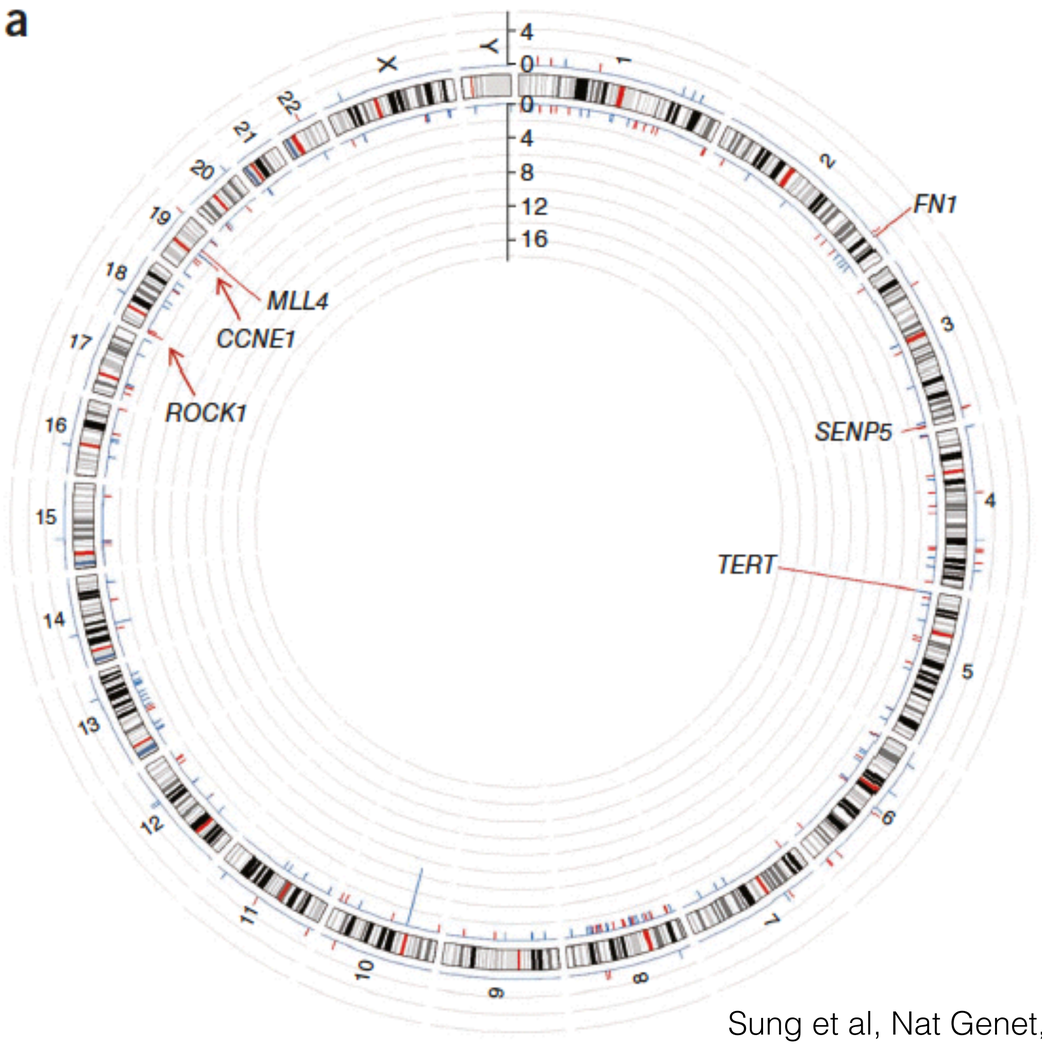
Direct mechanisms of HBV carcinogenesis

- Effects of viral proteins on oncogenic pathways
  - Large number of papers showing effects of HBV X and large S proteins on cell proliferation, apoptosis, sensitivity to mutagens, etc…, **but** no direct evidence from human tissue (data generated in mouse models or cell culture)

- Insertional mutagenesis
  - HBV DNA integration in cellular DNA from human HCCs first reported in 1980s
    Brechot et al, Nature, 1980; Chakraborty et al, Nature, 1980; Sharfitz et al, NEJM, 1981; Koshy, Cell, 1983
  - Consecutive studies showed that most HBV integrations are not recurrent

Whole-genome sequencing of HCCs

- WGS of 88 HCCs and adjacent non-tumor liver tissue from 81 HBV-positive and 7 HBV-negative patients from China
- 399 HBV integration breakpoints detected, randomly distributed across the whole genome, with some hotspots
- 344 occurred in HCCs, 55 in non-tumor tissue
- Only few genes with recurrent integration in HCCs:
  TERT (18/81), MLL4 (9/81), CCNE1 (4/81)



Sung et al, Nat Genet, 2012

HCV and HCC

- HCV does not integrate in the human genome
- HCV proteins have been implicated to regulate a large number of cellular processes, amongst them potential oncogenic pathways.
  - In cell culture (mostly using overexpression systems, but also HCV infection of Huh7 cells), HCV has been shown to
    - induce ER stress
    - oxidative stress
    - interact with p53
    - inhibit Rb
    - interfere with DNA damage repair
    - activate β-catenin
    - inhibit apoptosis

HCV and HCC

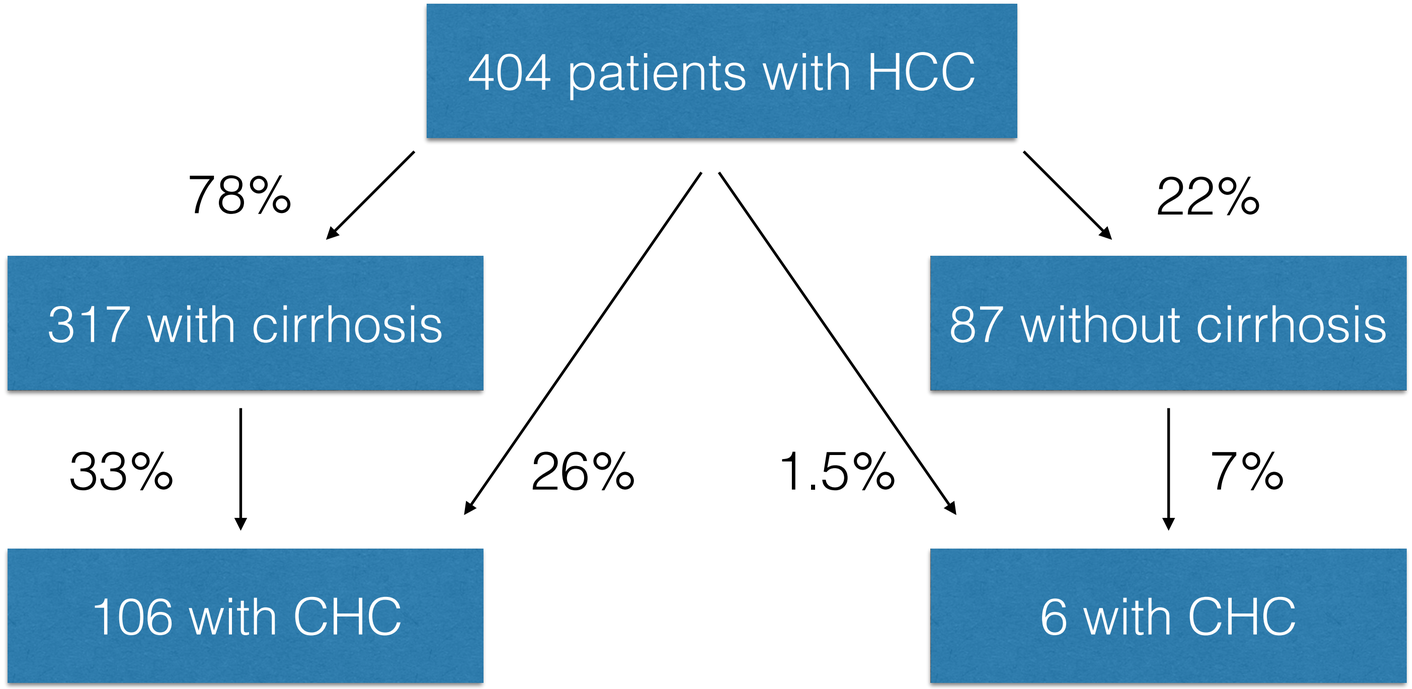
Table 2. Risk of cancer development in Japanese patients with hepatitis C (% per patient per year).

	Degree of fibrosis		
Chronic hepatitis	Mild	(F1)	0.5
	Moderate	(F2)	1.5
	Severe	(F3)	2.6
Cirrhosis		(F4)	5.8

Hiroaki Okuda, Best Practice & Research Clinical Gastroneterology, 2007

HCV associated HCC in non-cirrhotic livers

Retrospective analysis 404 patients with histologically proven HCC diagnosed in the Cleveland Clinic between 1994 and 2007



Albeldawi et al, Dig Dis Sci, 2012

Eradication of HCV and development of HCC

- Meta-analysis of 30 observational studies
  - 18 included all stages of fibrosis
  - 12 included advanced stages of fibrosis (F3 and F4, or F4 only)
  - 31’528 patients from 17 countries
  - average length of follow-up after treatment ranged from 2.5 - 14.4 years
  - overall, 35% of patients achieved SVR
  - in total, 1742 patients developed HCC (5.5%)

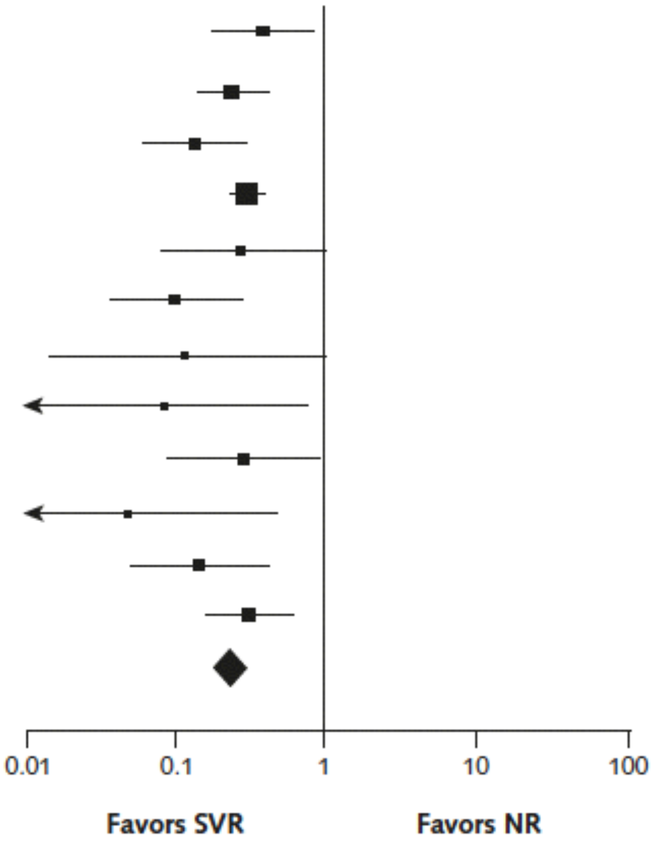
Morgan et al, Ann Int Med, 2013

Figure 1. Forest plot of adjusted hazard effects in persons at all stages of fibrosis.

Study, Year (Reference)	log(Hazard Ratio)	SE	Total		Weight, %	Hazard Ratio IV, Random (95% CI)
			SVR	NR		
Asahina et al, 2010 (36)	–0.944	0.388	686	1356	9.2	0.39 (0.18–0.83)
Hung et al, 2011 (46)	–1.423	0.273	1027	443	15.3	0.24 (0.14–0.41)
Kawamura et al, 2010 (50)	–1.985	0.407	1081	977	8.5	0.14 (0.06–0.31)
Kramer et al, 2011 (27)	–1.182	0.126	4292	10 276	31.2	0.31 (0.24–0.39)
Kurokawa et al, 2009 (51)	–1.277	0.631	139	264	4.0	0.28 (0.08–0.96)
Okanoue et al, 2002 (53)	–2.294	0.512	375	586	5.8	0.10 (0.04–0.28)
Osaki et al, 2012 (50)	–2.130	1.053	185	197	1.5	0.12 (0.02–0.94)
Pradat et al, 2007 (17)	–2.481	1.132	87	103	1.3	0.08 (0.01–0.77)
Sinn et al, 2008 (56)	–1.246	0.596	296	194	4.4	0.29 (0.09–0.93)
Takahashi et al, 2011 (57)	–3.022	1.163	89	114	1.3	0.05 (0.00–0.48)
Tateyama et al, 2011 (58)	–1.968	0.537	139	234	5.3	0.14 (0.05–0.40)
Yoshida et al, 1999 (61)	–1.164	0.324	789	1568	12.1	0.31 (0.17–0.59)
Total			9185	16 312	100.0	0.24 (0.18–0.31)

Heterogeneity: tau-square = 0.04; chi-square = 14.05; $P = 0.23$; $I^2 = 22\%$

Test for overall effect: $Z = 10.80$; $P < 0.001$



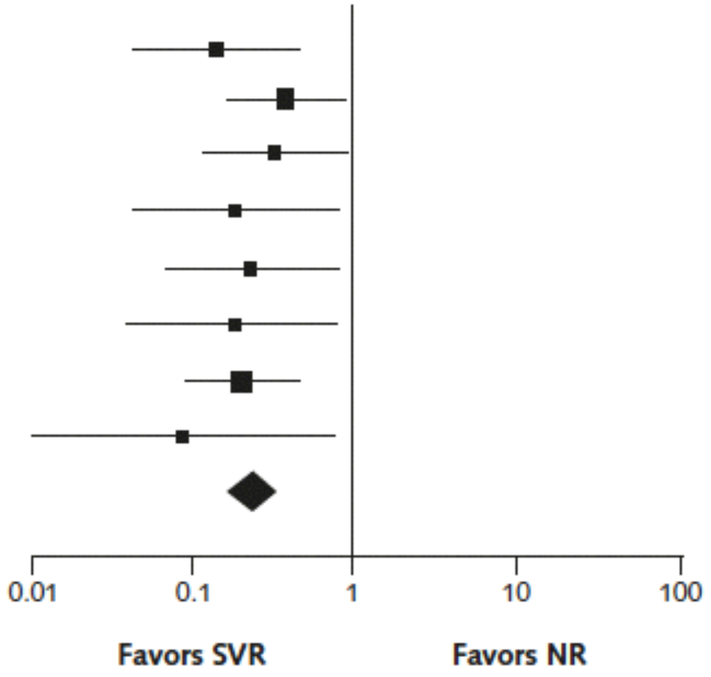
IV = inverse variance; NR = nonresponse; SVR = sustained virologic response.

Figure 2. Forest plot of adjusted hazard effects in persons with advanced liver disease.

Study, Year (Reference)	log(Hazard Ratio)	SE	Total		Weight, %	Hazard Ratio IV, Random (95% CI)
			SVR	NR		
Braks et al, 2007 (37)	–1.966	0.601	37	76	11.2	0.14 (0.04–0.45)
Bruno et al, 2007 (38)	–0.954	0.425	124	759	22.4	0.39 (0.17–0.89)
Cardoso et al, 2010 (40)	–1.120	0.514	103	204	15.3	0.33 (0.12–0.89)
Hasegawa et al, 2007 (64)	–1.690	0.755	48	57	7.1	0.18 (0.04–0.81)
Hung et al, 2006 (65)	–1.468	0.622	73	59	10.4	0.23 (0.07–0.78)
Morgan et al, 2010 (52)	–1.721	0.764	140	309	6.9	0.18 (0.04–0.80)
van der Meer et al, 2012 (63)	–1.592	0.416	192	338	23.4	0.20 (0.09–0.46)
Velosa et al, 2011 (60)	–2.433	1.108	39	91	3.3	0.09 (0.01–0.77)
Total			756	1893	100.0	0.23 (0.16–0.35)

Heterogeneity: tau-square = 0.00; chi-square = 3.64; $P = 0.82$; $I^2 = 0\%$

Test for overall effect: $Z = 7.21$; $P < 0.001$



IV = inverse variance; NR = nonresponse; SVR = sustained virologic response.

Morgan et al, Ann Int Med, 2013

HCV-SVR and HCC

	F3-F4	All stages of fibrosis
Number of patients	2649	25497
HCCs in patients with SVR	32 (of 756 = 4.2%)	145 (of 9185 = 1.5%)
HCCs in non-responders	337 (of 1893 =17.8%)	990 (of 16312 = 6.2%)
Absolute Risk Reduction	13.6%	4.7%
Hazard Ratio	0.23	0.24

Morgan et al, Ann Int Med, 2013

Direct versus Indirect:
Existing data can not resolve the controversy

- Correlation of HBV viral load with HCC incidence could result from an increased number of infected hepatocytes (direct) but also from an increased necroinflammatory activity (indirect)

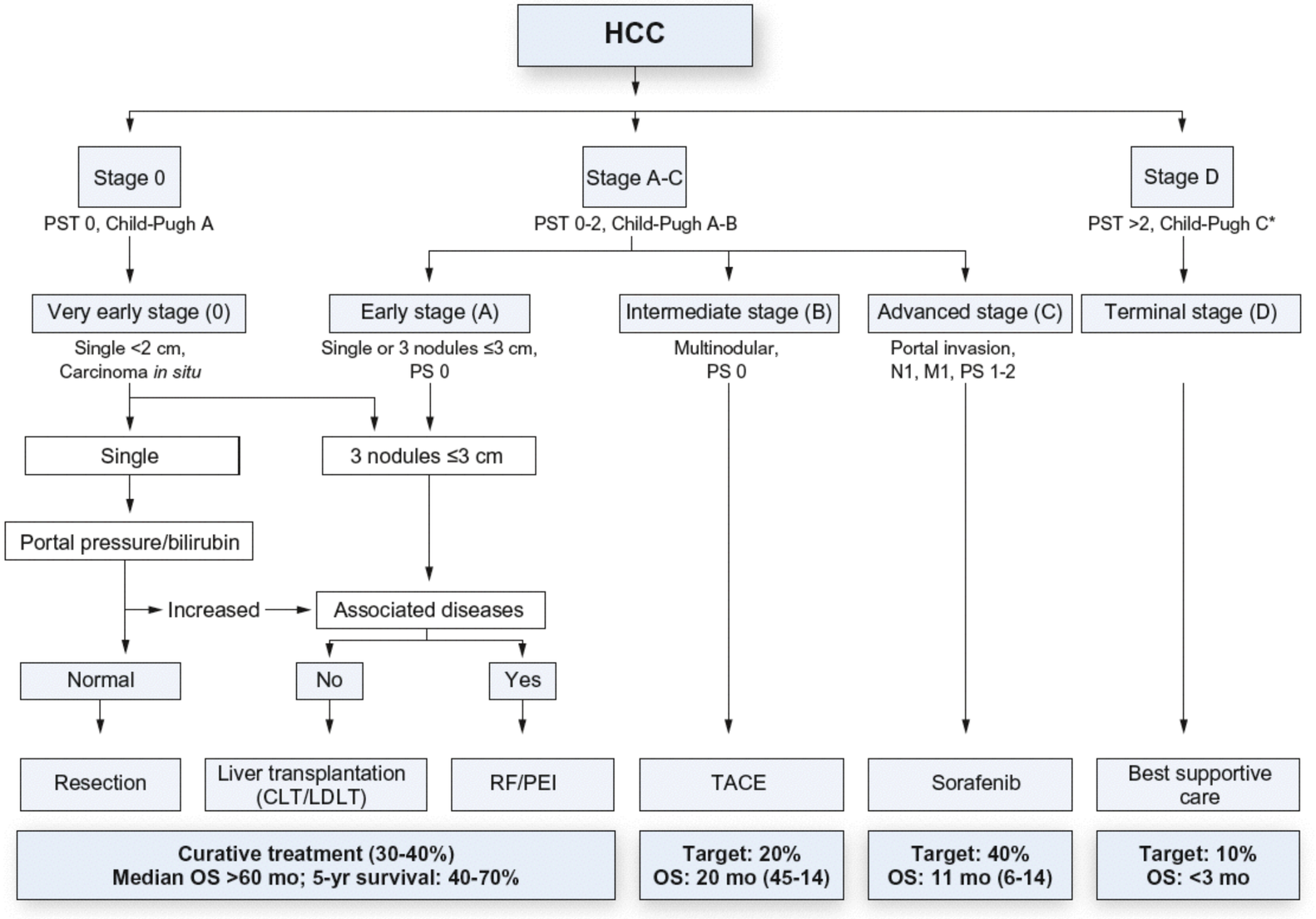
- Treatment induced inhibition of HBV or eradication of HCV could result in less direct damage to infected cells (direct) but also reduce necroinflammatory activity (indirect)

- Even with next generation sequencing -omics data, HBV insertional mutagenesis has not be convincingly proven so far

- All animal models of virus associated HCCs have important differences to human HCCs and therefore limited significance for the human disease

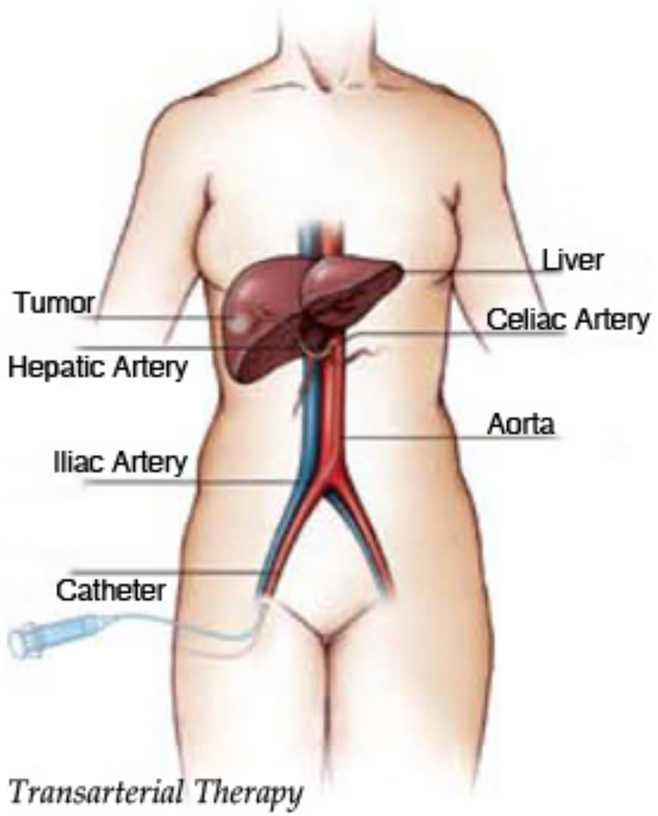
HCC in the era of cancer -omics

- Compared to other common cancers, HCC -omics is years behind
- The practice of non-invasive diagnosis of HCC results in a scarcity of HCC tissue samples for research purposes
- Most published -omics data are based on resected HCCs
- As of 2016, there is no meaningful molecular classification of HCC
- meaningful = allows to recruit patients for “targeted” therapies

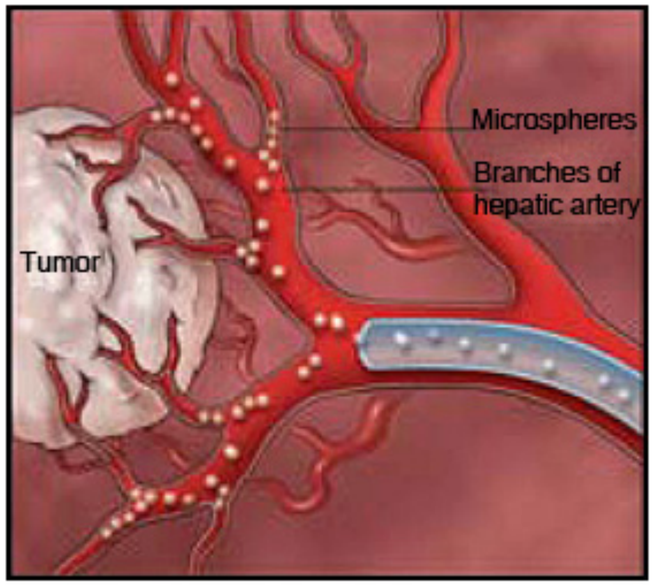


EASL–EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma, Journal of Hepatology 2012

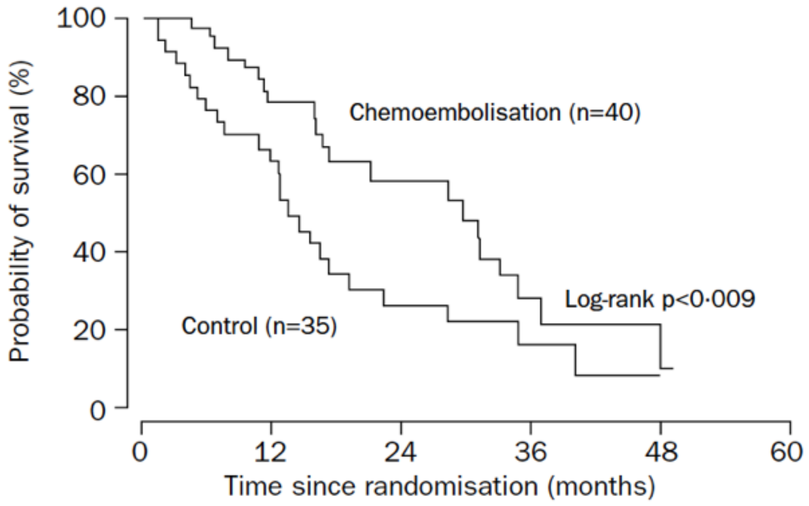
Transarterial Chemoembolisation



Transarterial Therapy



Microspheres injected during transarterial therapy "lock in" chemotherapy.

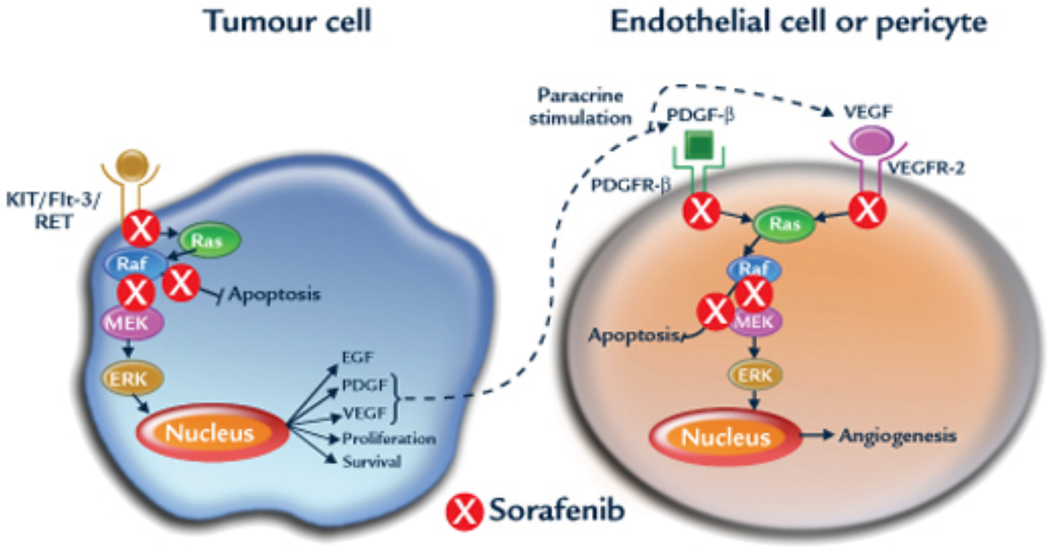


Patients at risk

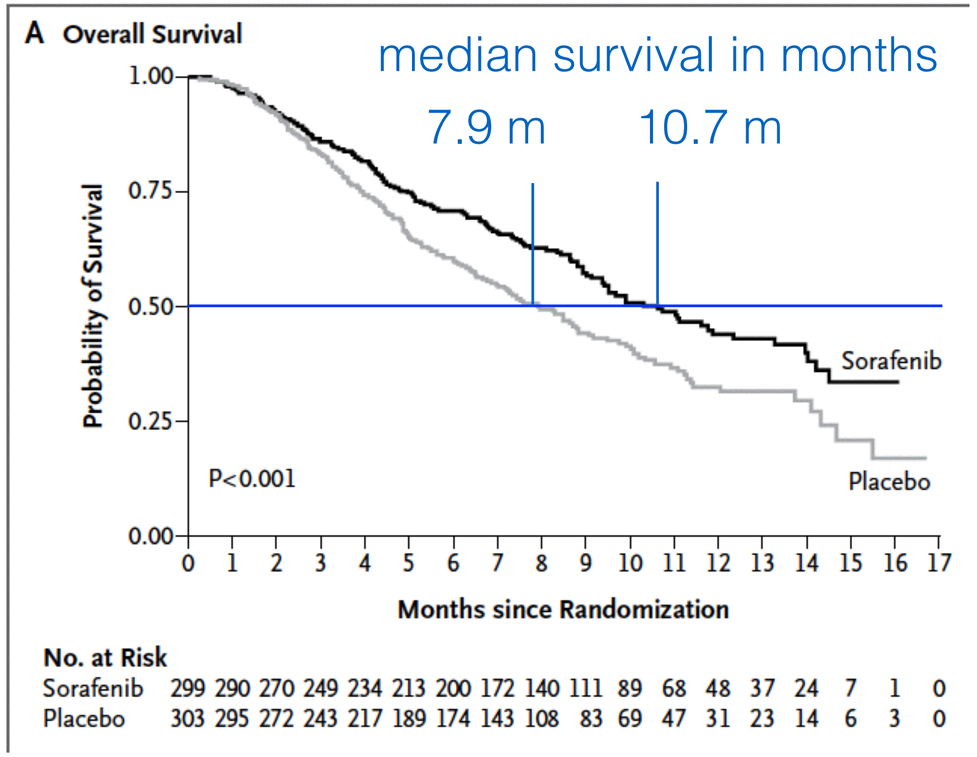
Chemoembolisation	40	29	14	4	2
Control	35	19	7	3	0

Bruix et al, Lancet, 2002

Sorafenib (Nexavar®)



Multikinase inhibitor: VEGFR, PDGFR, RAF kinases (RAF/MEK/ERK pathway)



Llovet et al, NEJM, 2008

Systemic therapy of HCC

- No conventional systemic chemotherapy has provided response rates > 25%, and none has provided improved overall survival.

  Tested drugs include: doxorubicin, cisplatin, cisplatin, 5-fluorouracil, mitoxantrone, etoposide, fludarabine, paclitaxel, irinotecan, gemcitabine, capecitabine, tamoxifen, antiandrogens, octreotide, thalidomide (reviewed in Wörns et al, Dig Dis 2009)

- Several targeted agents have been tested in phase III trials. None was found to be superior to Sorafenib, and none was found to be active against Sorafenib resistant HCCs.

  Agents include: Sunitinib, Linifanib, Brivanib, Lenvatinib, Everolimus, Ramucirumab, Regorafenib, Tivantinib, Cabozantinib (reviewed in Wörns and Galle, Nat Rev Gastroenterol Hepatol 2014)

Cancer Genomes and Driver Genes

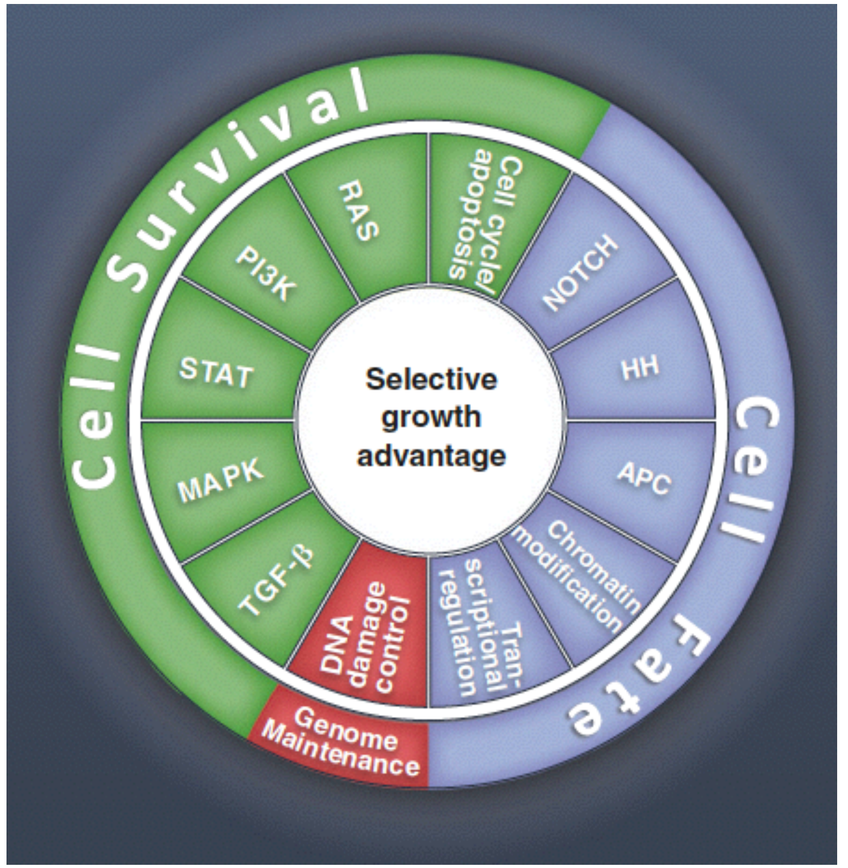
- In common solid tumors, an average of 33-66 somatic genes genes display somatic mutations that would be expected to alter their protein products (Vogelstein et al, Science, 2013)

- Driver gene mutations (drivers) confer directly or indirectly a selective growth advantage to the cell in which it occurs.
  Passenger mutations (passengers) have no direct or indirect effect on the selective growth advantage

- Genome-wide sequencing studies of 3284 tumors have discovered 138 driver genes: 74 are tumor suppressor genes and 64 are oncogenes (Vogelstein et al, Science, 2013)

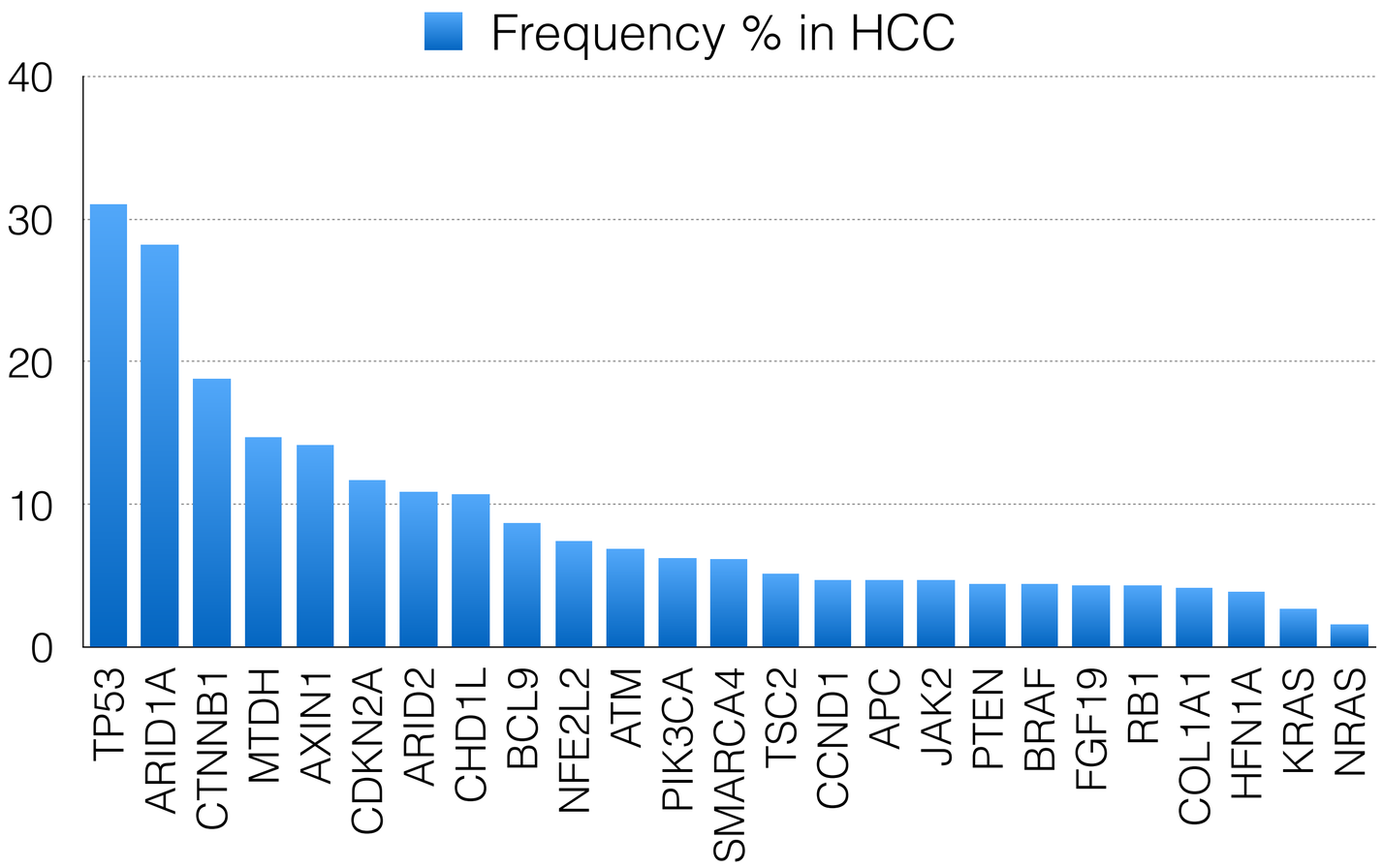
Oncogenic signaling pathways

- All known driver genes can be classified in one or more of 12 signalling pathways
- These pathways can be be further organised into three core cellular processes:
  - Cell fate
  - Cell survival
  - Genome maintenance



Vogelstein et al, Science, 2013

“Long tails”



Shibata and Aburatani, Nat Rev Gastro Hepatol, 2014

- “For many cancer types, a handful of cancer genes are mutated at high frequency, but many more cancer-related genes are found mutated at much lower frequencies” (“long tails”)

Vogelstein et al, Science, 2013

Liver cancer genomes

- HCCs are genetically heterogeneous

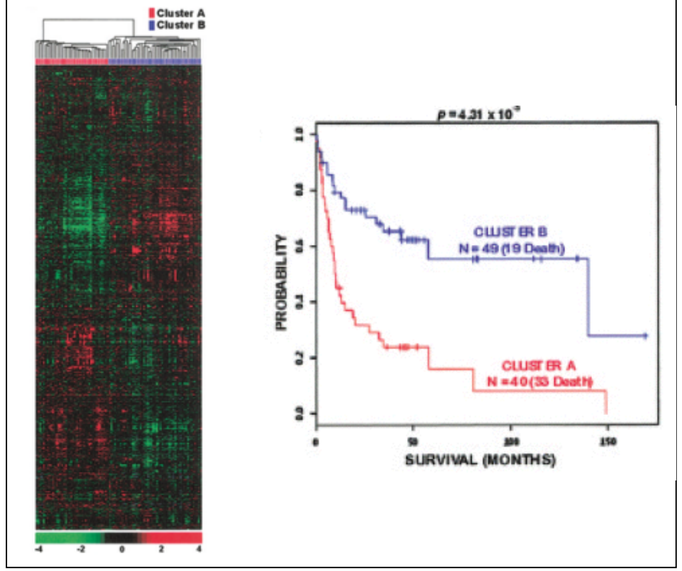
- The published data are only partially overlapping, and the reason for low level of reproducibility of data are unclear (technical issues, patient selection, stochastics, small sample sizes, true heterogeneity)
  Li et al, Nat Genet, 2011; Huang et al, Nat Genet, 2012; Fujimoto et al, Nat Genet, 2012; Guichard et al, Nat Genet, 2012Kan et al, Genome Research, 2013; Cleary et al, Hepatology, 2013
  (In total, 140 samples with exome sequencing and 113 samples with whole genome sequencing)

- A molecular classification that divides HCCs in groups with distinct (and potentially drugable) oncogenic driver pathways has not been derived so far from genomic analysis of HCCs

Transcriptome based molecular classification

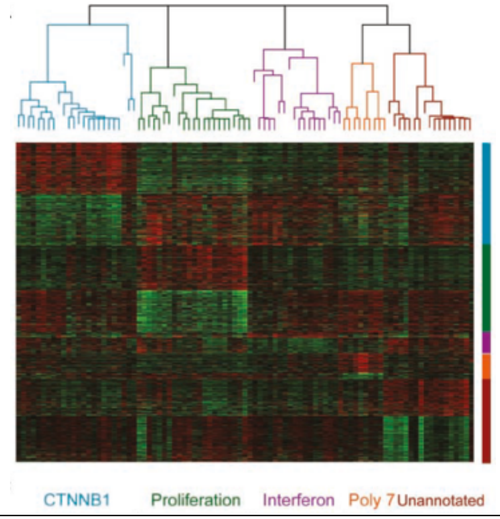
Lee et al (Thorgeirsson)
Hepatology 2004

- 91 surgically resected HCC specimens from 90 patients from China and Belgium
- transcriptome analysis with microarrays → 2 groups



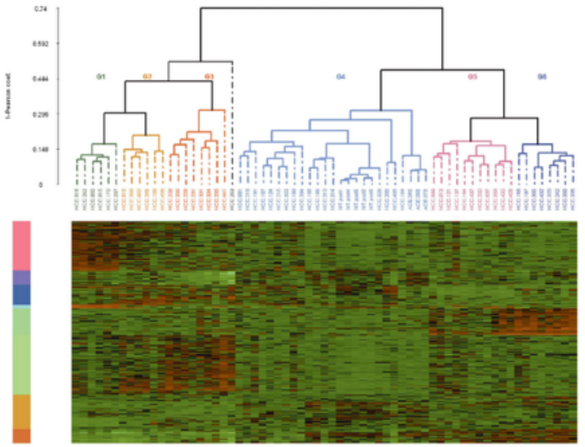
Chiang et al (LLovet)
Cancer Res 2008

- 103 surgically resected/liver explanted HCC specimens from 100 patients from Barcelona, Milano or New York
- transcriptome analysis (Affymetrix U133 Plus 2.0) → 5 groups



Boyault et al (Zucman-Rossi)
Hepatology 2007

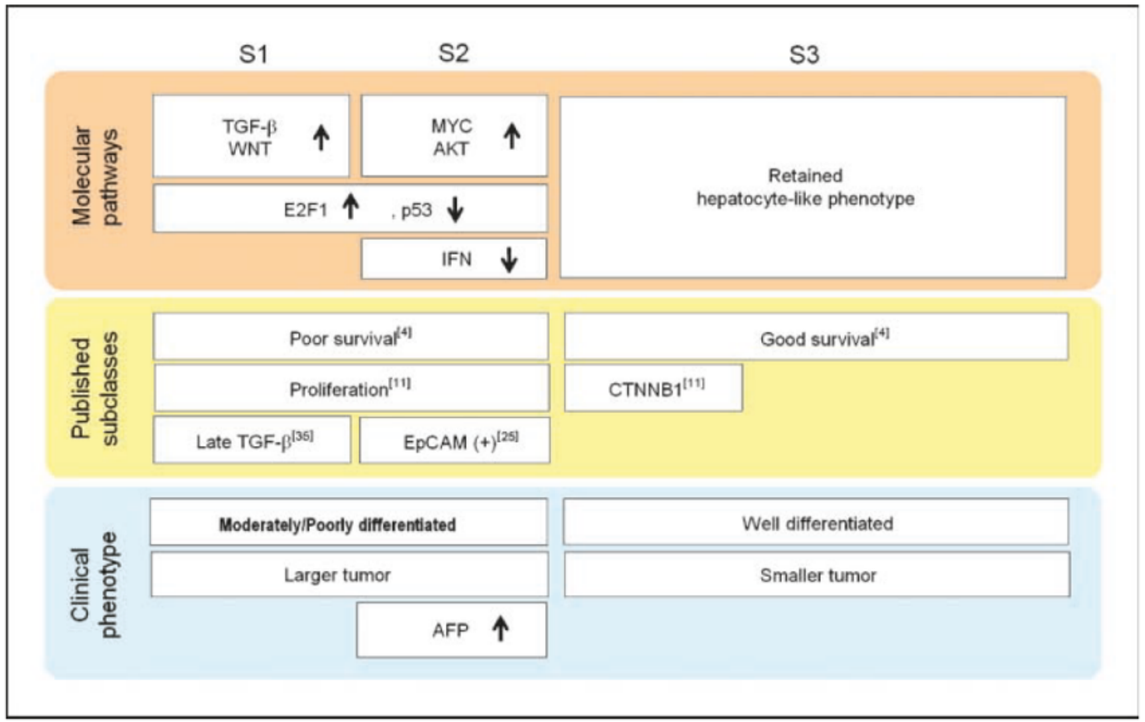
- 57 surgically resected HCC specimens
- transcriptome analysis (Affymetrix HG-U133) → 6 groups (G1-G6)



Integrative Transcriptome Analysis Reveals Common Molecular Subclasses of Human Hepatocellular Carcinoma

Yujin Hoshida,[1,2] Sebastian M.B. Nijman,[1,5] Masahiro Kobayashi,[6] Jennifer A. Chan,[1,7] Jean-Philippe Brunet,[1] Derek Y. Chiang,[1] Augusto Villanueva,[8] Philippa Newell,[10] Kenji Ikeda,[6] Masaji Hashimoto,[6] Goro Watanabe,[6] Stacey Gabriel,[1] Scott L. Friedman,[10] Hiromitsu Kumada,[6] Josep M. Llovet,[8,9,10] and Todd R. Golub[1,2,3,4]

- meta-analysis of gene expression profiles in data sets from eight independent patient cohorts across the world
- → 3 robust subclasses: S1, S2, S3
- analysis of components of the signatures indicated that
  - S1 = activation of WNT-βcatenin pathway
  - S2 = proliferation, MYC and AKT activation
  - S3 = hepatocyte differentiation



activation, thus representing a new mechanism of WNT pathway activation in HCC. These experiments establish the first consensus classification framework for HCC based on gene expression profiles and highlight the power of integrating multiple data sets to define a robust molecular taxonomy of the disease. [Cancer Res 2009;69(18):7385–92]

Cancer Res 2009

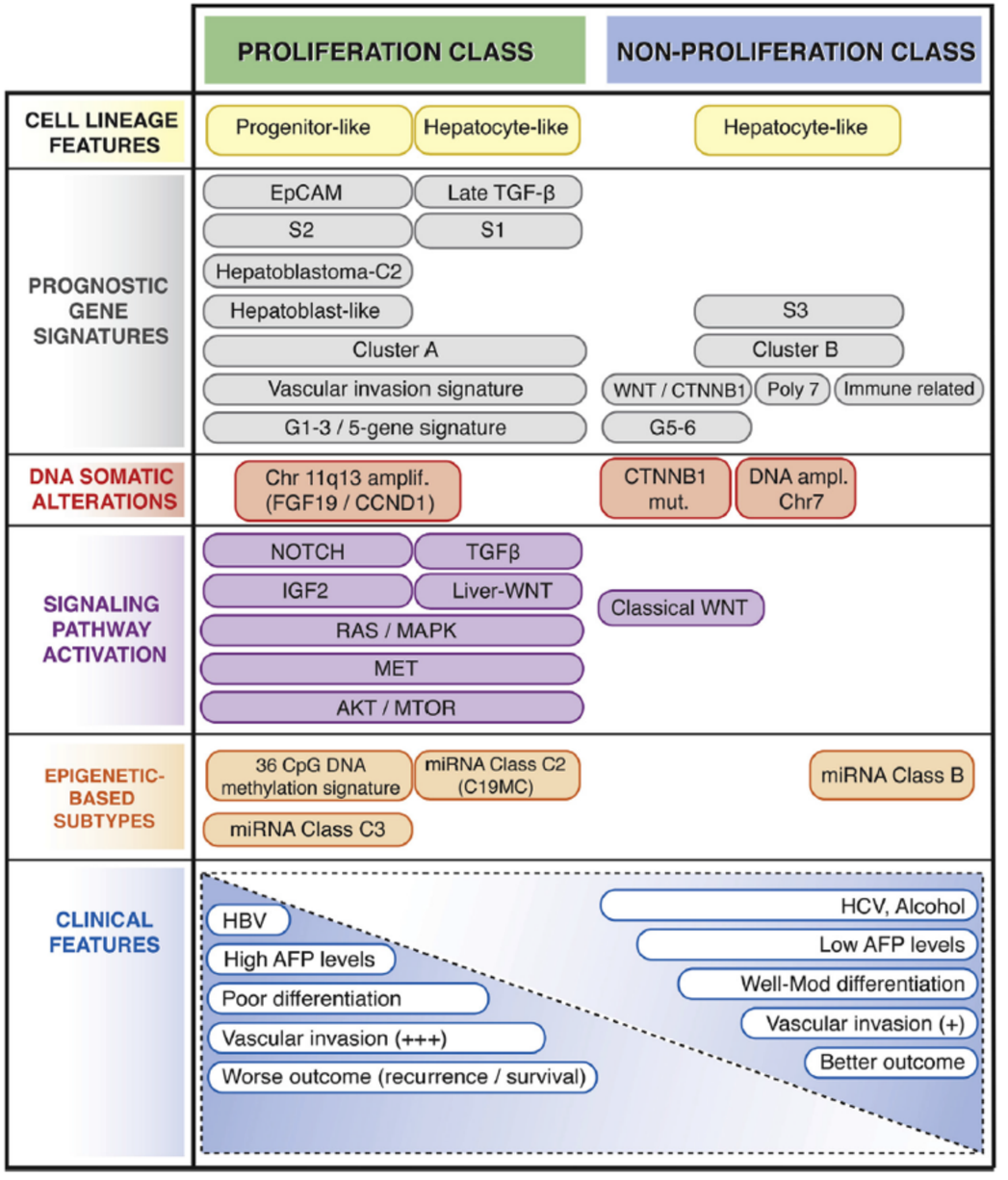
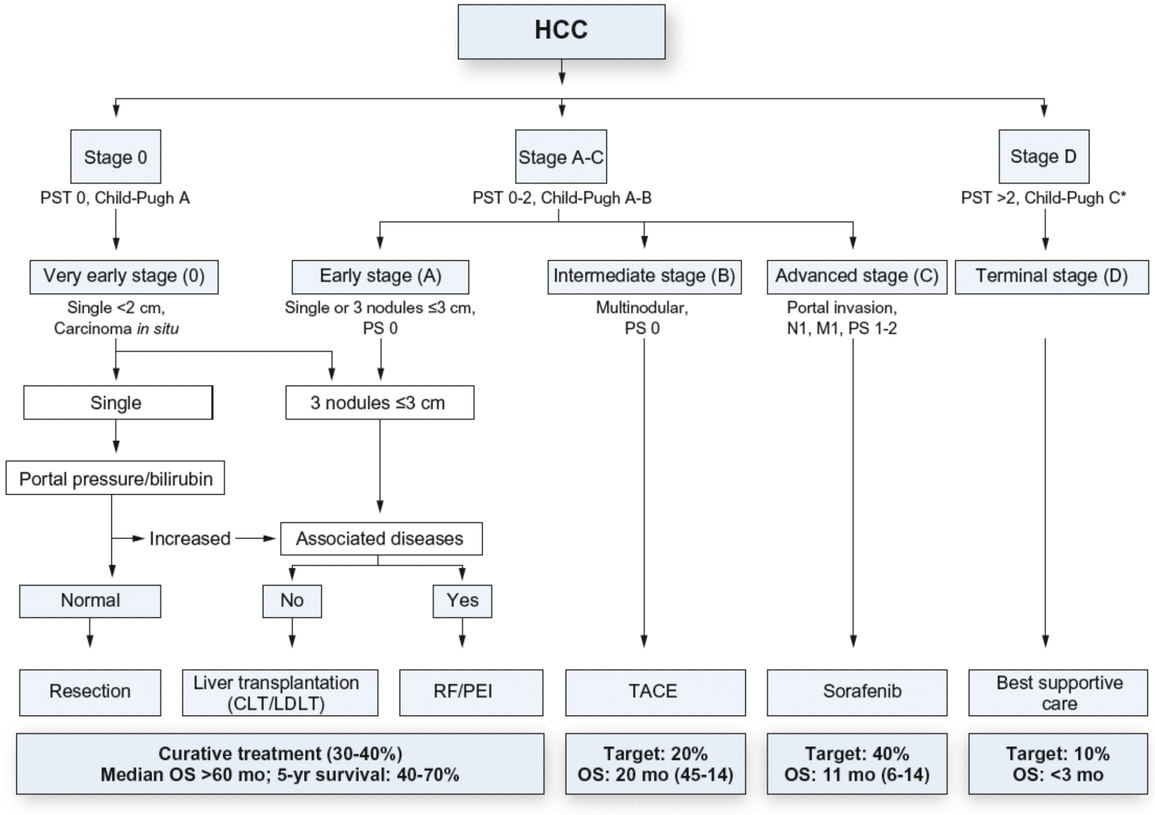


Figure 4. Summary of molecular classification of HCC. Major classes (proliferation and nonproliferation) are depicted based on messenger RNA expression profiling. Additional molecular features affecting DNA structure, pathway deregulation and epigenetics are overlapped.

Zucman-Rossi, Villanueva, Nault and Llovet, Gastroenterology, 2015

Barcelona Clinic Liver Cancer (BCLC) classification

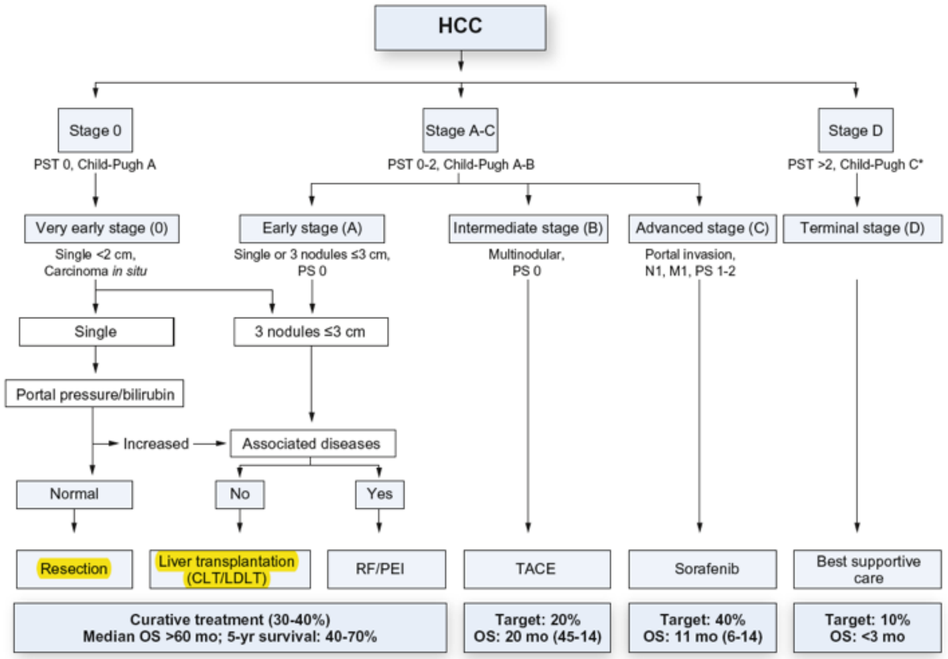


- Staging systems in HCC should define outcome prediction and treatment assignment. They should facilitate exchange of information, prognosis prediction and trial design. Due to the nature of HCC, the main prognostic variables are tumor stage, liver function and performance status
- The BCLC staging system is recommended for prognostic prediction and treatment allocation **(evidence 2A; recommendation 1B)**. This staging system can be applied to most HCC patients, as long as specific considerations for special subpopulations (liver transplantation) are incorporated
- Refinement of BCLC class C by clinical or biomarker tools should further facilitate understanding of outcome data and trial stratification
- Other staging systems applied alone or in combination with BCLC are not recommended in clinical practice
- Molecular classification of HCC based on gene signatures or molecular abnormalities is not ready for clinical application **(evidence 2A; recommendation 1B)**

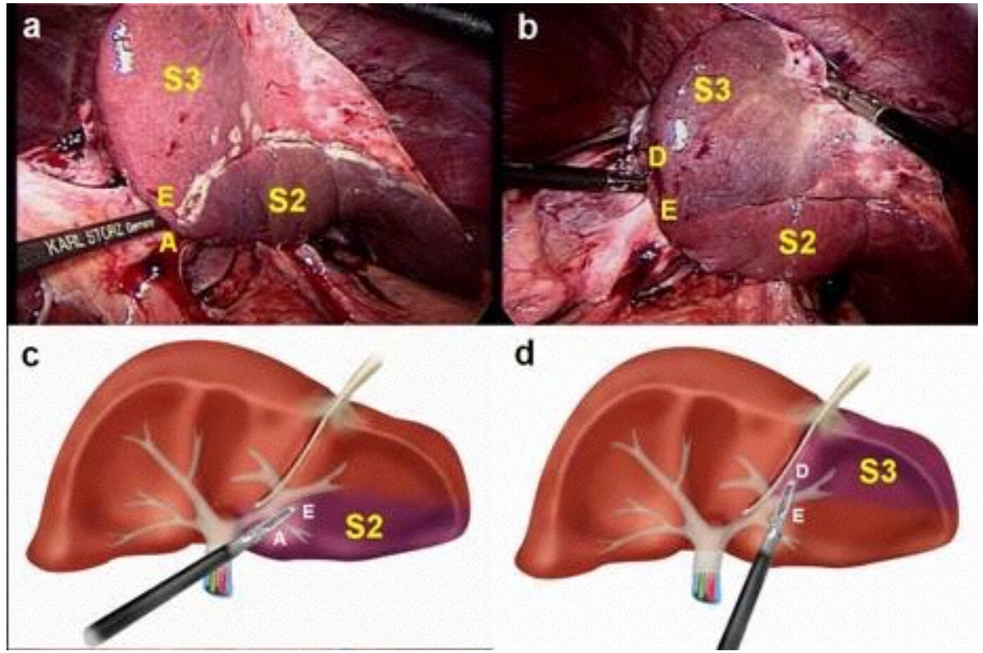
EASL–EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma, Journal of Hepatology 2012

Shortcomings of the existing molecular classification systems

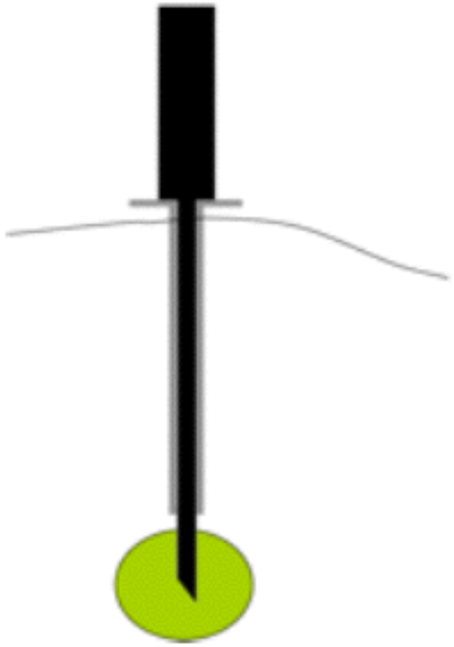
Selection Bias



Sample Preparation/Quality



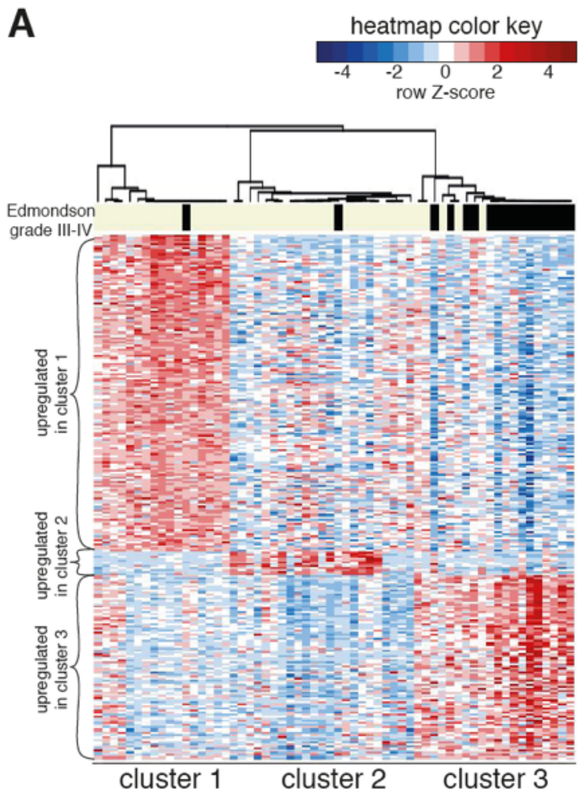
US-guided liver biopsy procedure



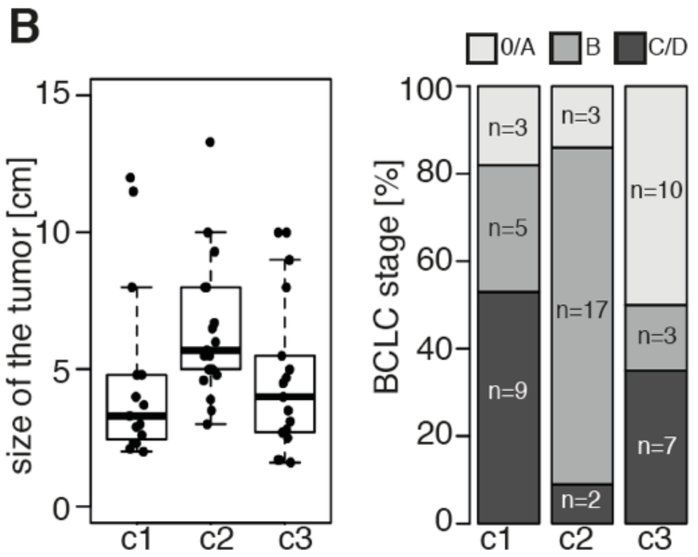
- 60 patients with HCC included from 2002-2012
- Biopsies of tumor and non-tumor liver
- Transcriptome analysis with Affymetrix Human Gene ST 1.0 microarrays
- Statistical analysis with Bioconductor/R and javaGSEA

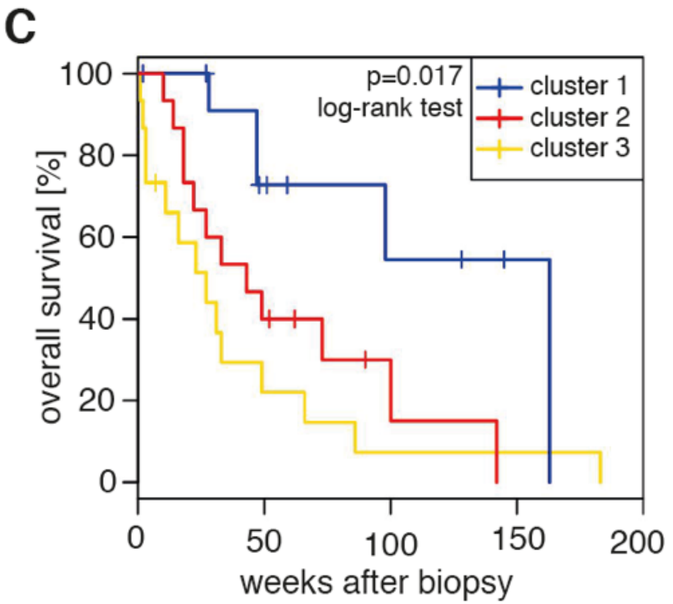
Makowska et al, J Pathol Clin Res, 2016

Consensus clustering of gene expression profiles



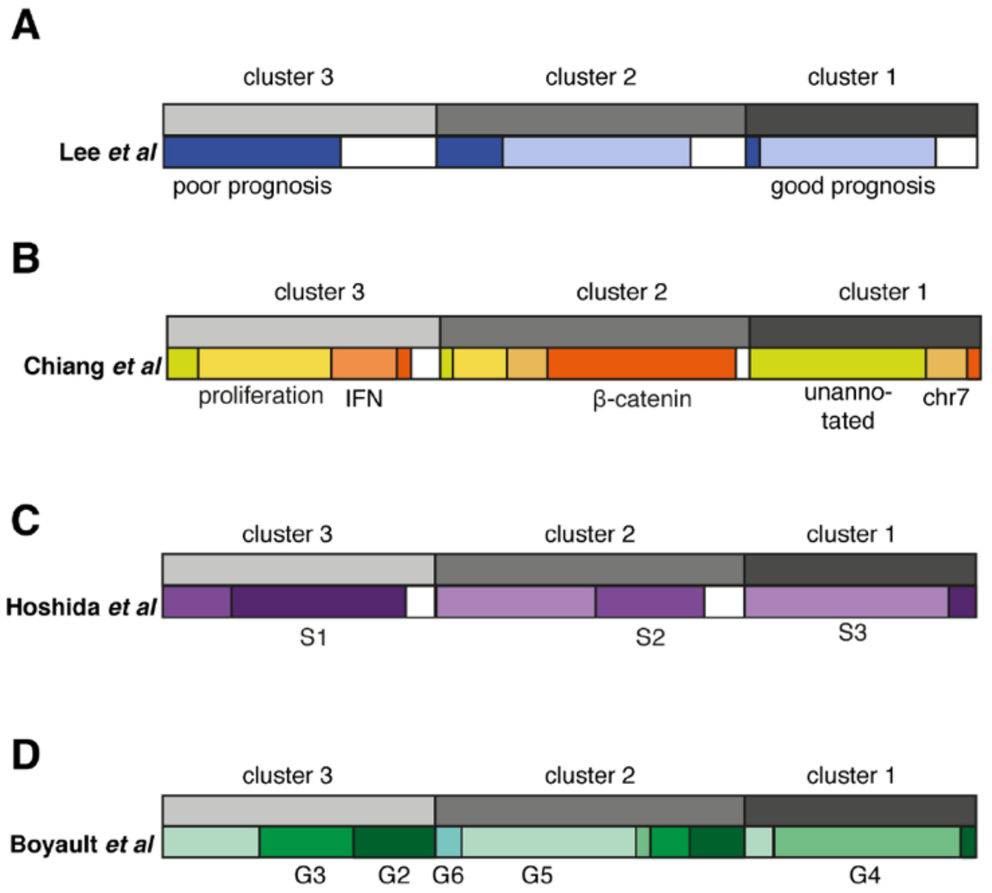
Z-score values show
standard deviations from the mean expression value





Makowska et al, J Pathol Clin Res, 2016

Overlaps between different classification systems

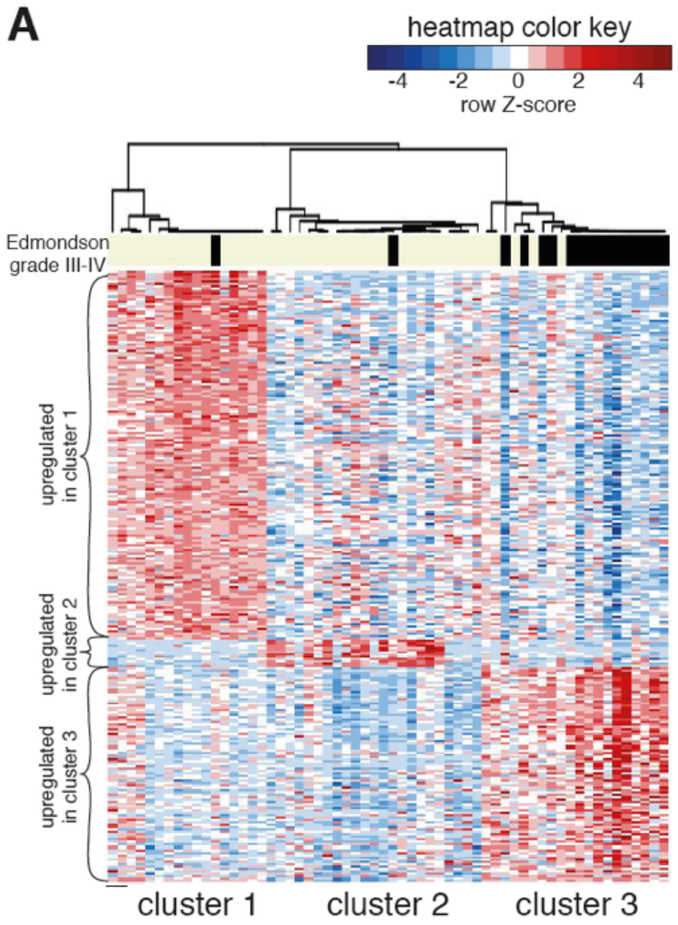


Conclusion:

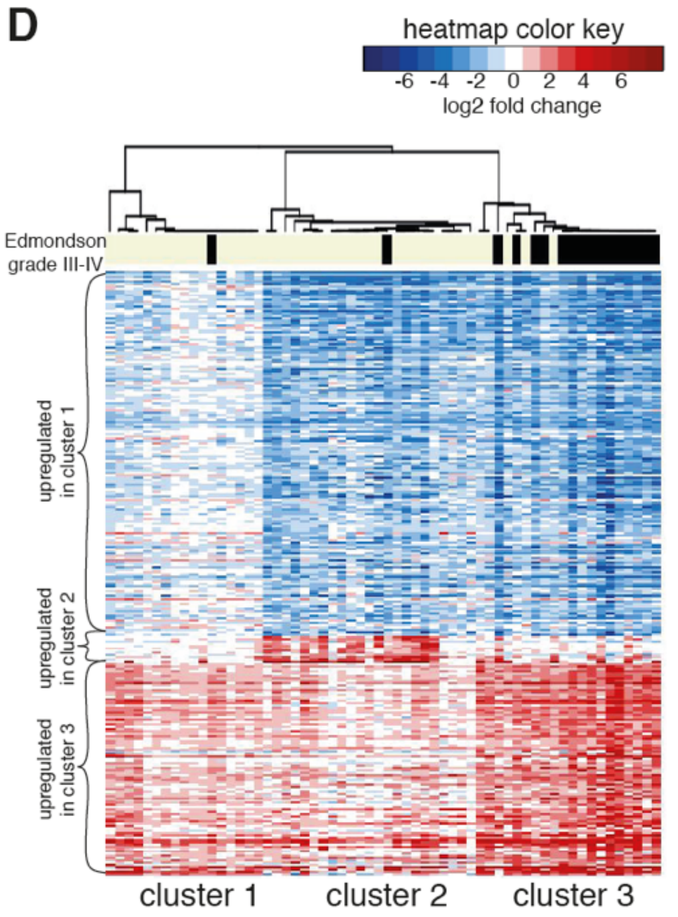
- Despite the differences in sample handling and processing and in tumor stage distribution in the study populations, most samples can be assigned to the classes of published classification systems with high confidence
- This demonstrates the usefulness of gene expression data from surgical resection specimens
- But once again the consensus between the classification system is limited, highlighting the important problem of lack of reproducibility between different classification systems

Makowska et al, J Pathol Clin Res, 2016

A second look at consensus clustering

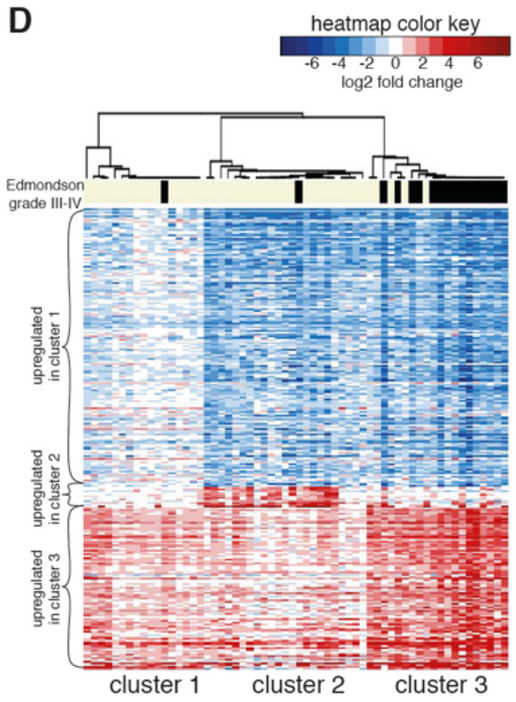


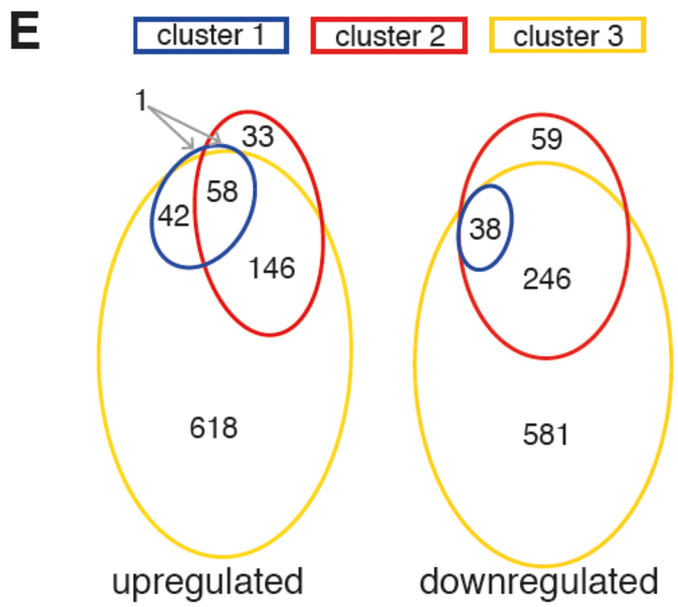
Z-score values show standard deviations from the mean expression value of HCC samples

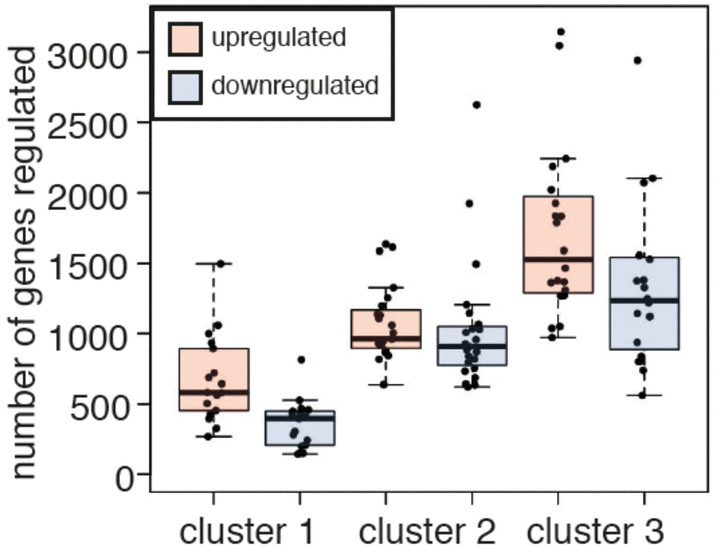


Z-score values show standard deviations from the mean expression value of 5 healthy liver control samples

Quantitative rather than qualitative differences of gene expression define the clusters



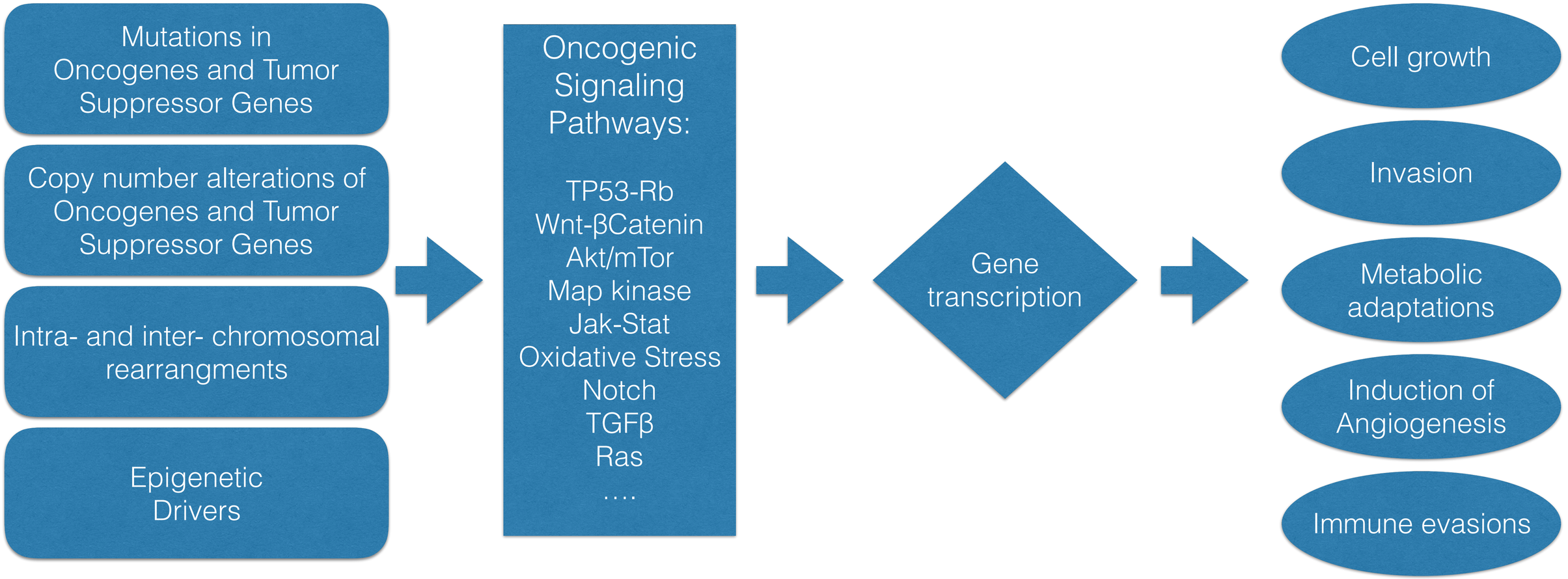




Makowska et al, J Pathol Clin Res, 2016

mRNA expression profiling of HCCs

- Several classification systems published, but no consensus
- None of the systems identifies meaningful subgroups with distinct oncogenic driver pathways
- The added value of transcriptome analysis over classical histopathological grading and quantification of cell proliferation with immunostaining for Ki67 is not known



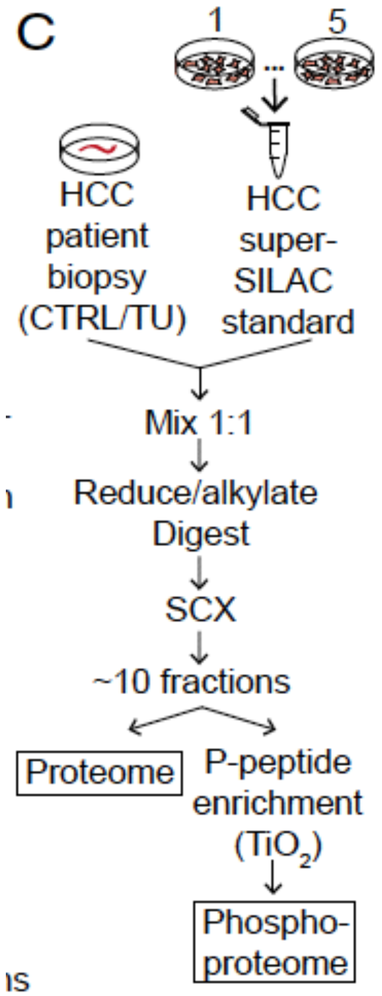
- Exome sequencing
- Whole genome sequencing
- Genome-wide DNA methylation analysis

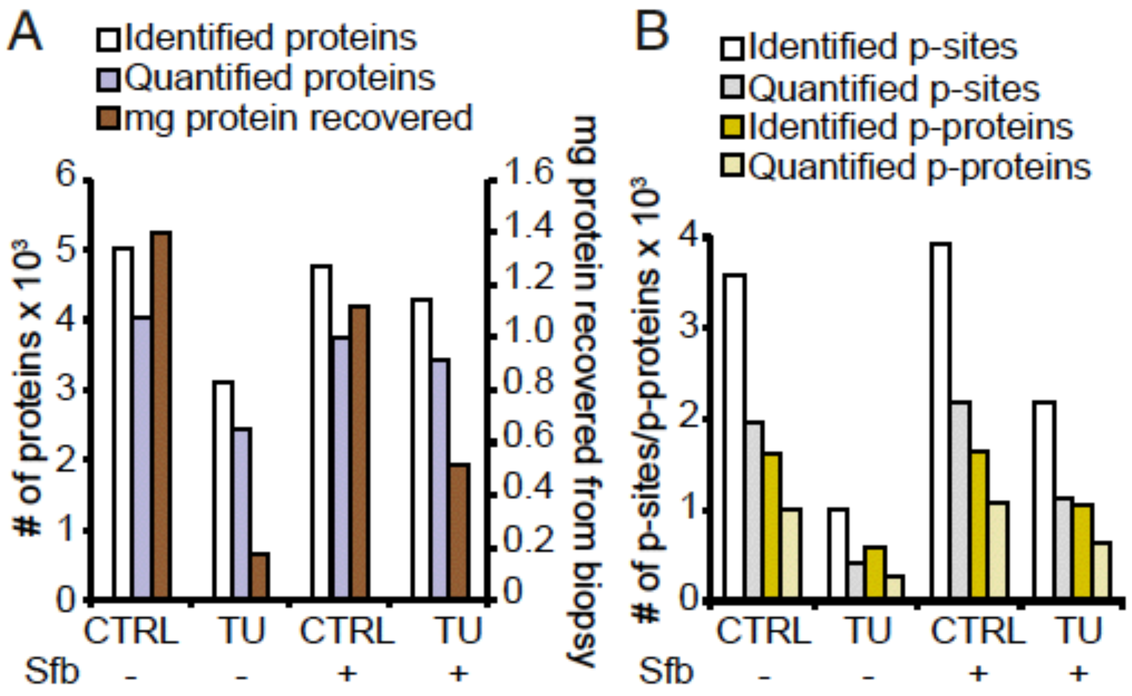
- Phosphoproteomics

- Transcriptomics

- Proteomics
- Lipidomics
- Metabolomics

Phosphoproteomics with HCC biopsies





Dazert et al, PNAS, 2016

Quantitative proteomics and phosphoproteomics on serial tumor biopsies from a sorafenib-treated HCC patient

Eva Dazert[a], Marco Colombi[a], Tujana Boldanova[b], Suzette Moes[a], David Adametz[c], Luca Quagliata[d], Volker Roth[c], Luigi Terracciano[d], Markus H. Heim[b], Paul Jenoe[a], and Michael N. Hall[a,1]

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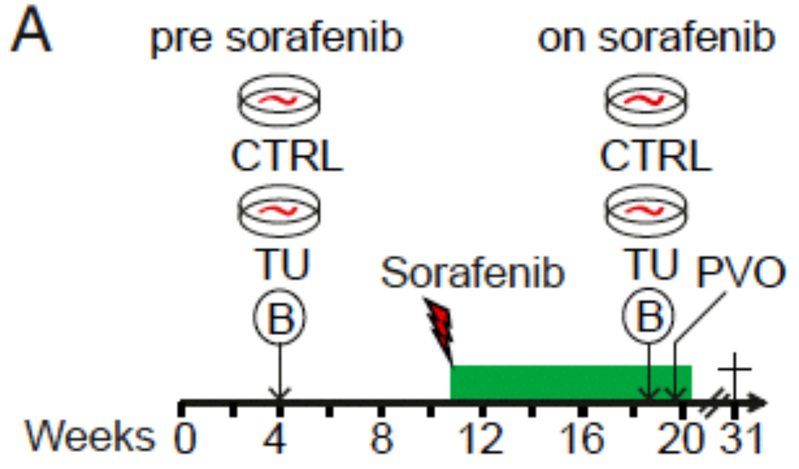

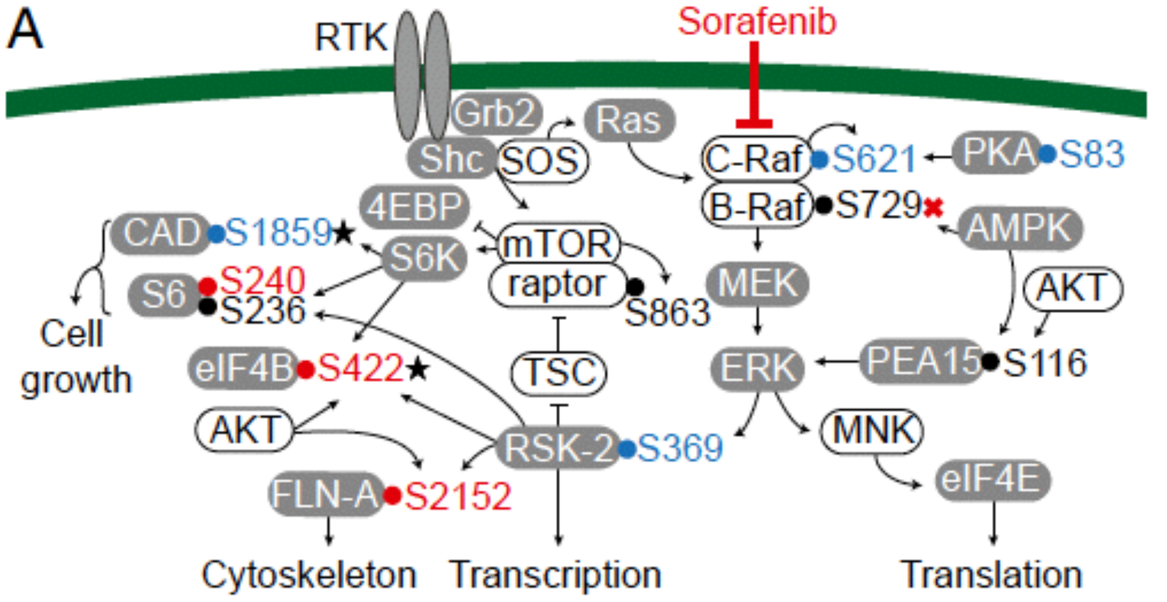

Outlook

- Molecular characterisation of a HCCs by integrating genomic, transcriptomic, proteomic, phosphoproteomic, and metabolomic data
- Generation of patient derived xenograft mouse models (PDX mice)
- Generation of patient derived cell culture models

Mutations in Oncogenes and Tumor Suppressor Genes

Copy number alterations of Oncogenes and Tumor Suppressor Genes

Intra- and inter- chromosomal rearrangments

Epigenetic Drivers

HDAC inhibitors

DNA methyltransferase inhibitors

- sequencing
- Genome-wide DNA methylation analysis

Oncogenic Signaling Pathways:

Antibodies to growth factor receptors

Akt/mTor
Map kinase
Jak-Stat

Kinase inhibitors

Notch
TGFβ
Ras
….

- Phosphoproteomics

Gene transcription

siRNAs

- Transcriptomics

Cell growth

Interfering with cancer specific metabolism

Metabolic adaptations

Induction of Angiogenesis

Angiogenesis inhibitors

Immune evasions

Immune checkpoint inhibitors

- Proteomics
- Lipidomics
- Metabolomics

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