

Hepatocellular Carcinoma

(in the non-cirrhotic liver)



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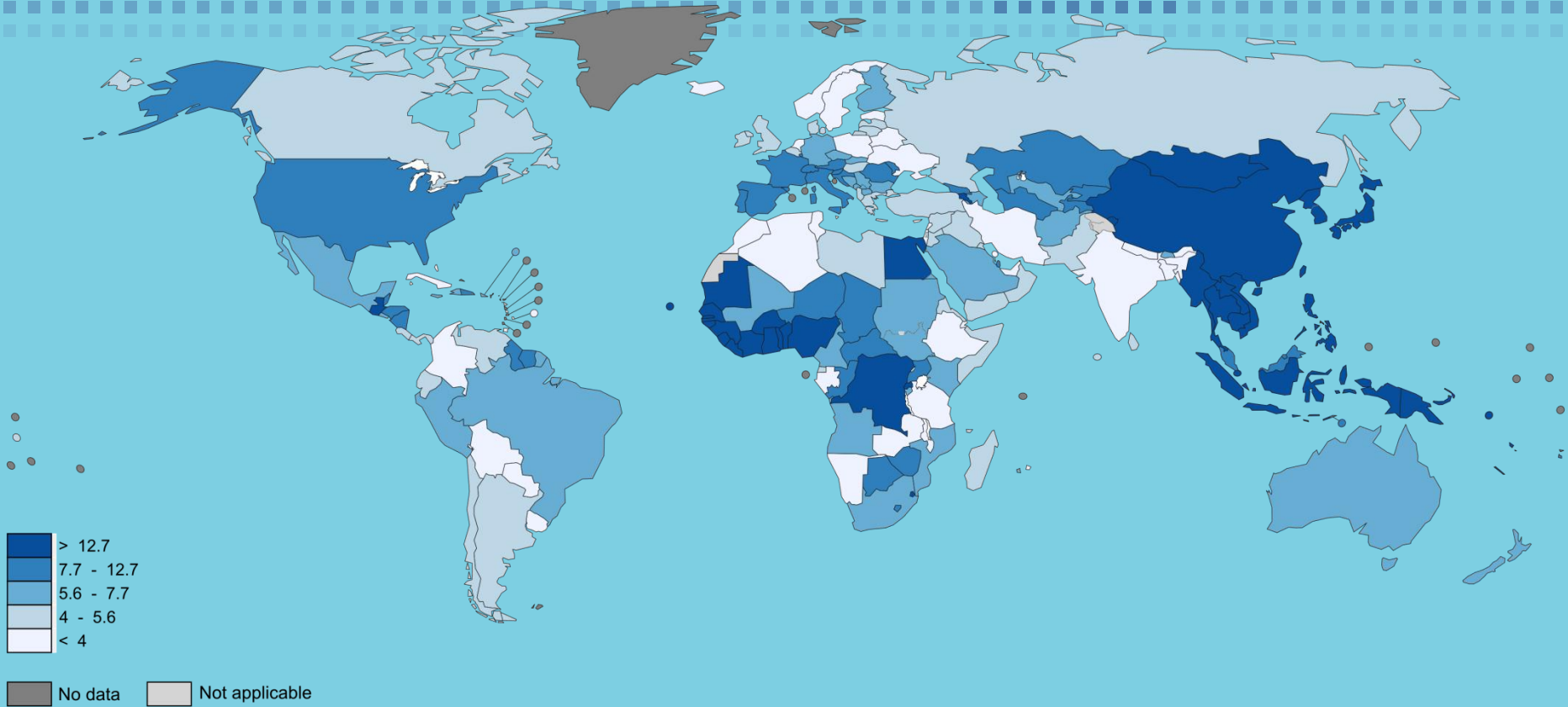
Rotterdam, The Netherlands

1st Maastricht E-AHPBA Post-Graduate HPB Course

Maastricht June 2-3, 2016

- HCC is the **sixth** most common neoplasm.
- HCC results in between **+/- one million deaths** globally per annum (**third** leading cause of **cancer-related death** in the world)
- **Almost 80% cases are due to underlying liver cirrhosis** (chronic HBV or HCV infection) and consequently **20% HCC develops in non-cirrhotic livers**
- Compensated cirrhosis have a **3-4% annual incidence of HCC**, and those with chronic hepatitis have an approximate annual risk of **1%**

Epidemiology



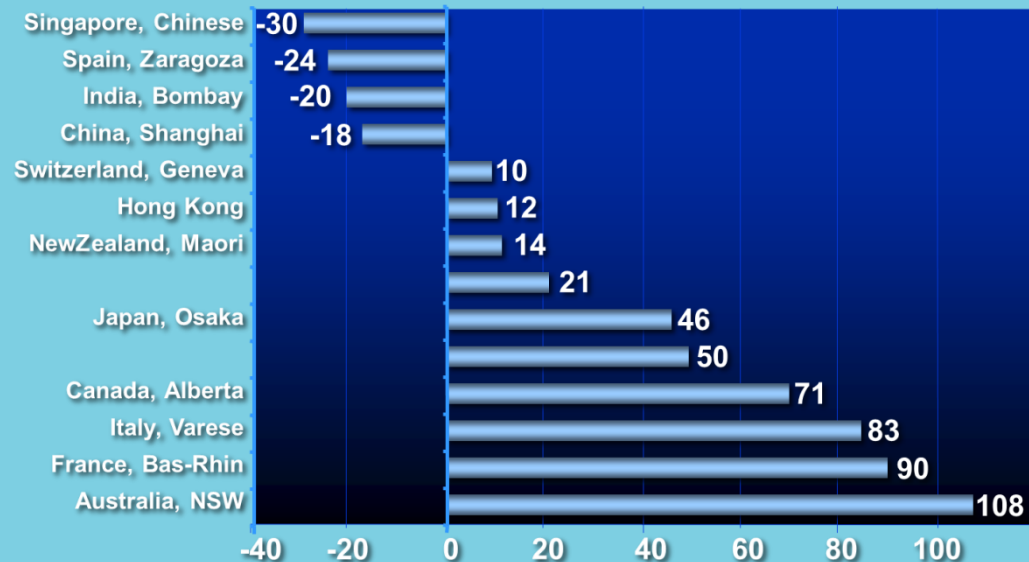
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Map production: IARC
World Health Organization



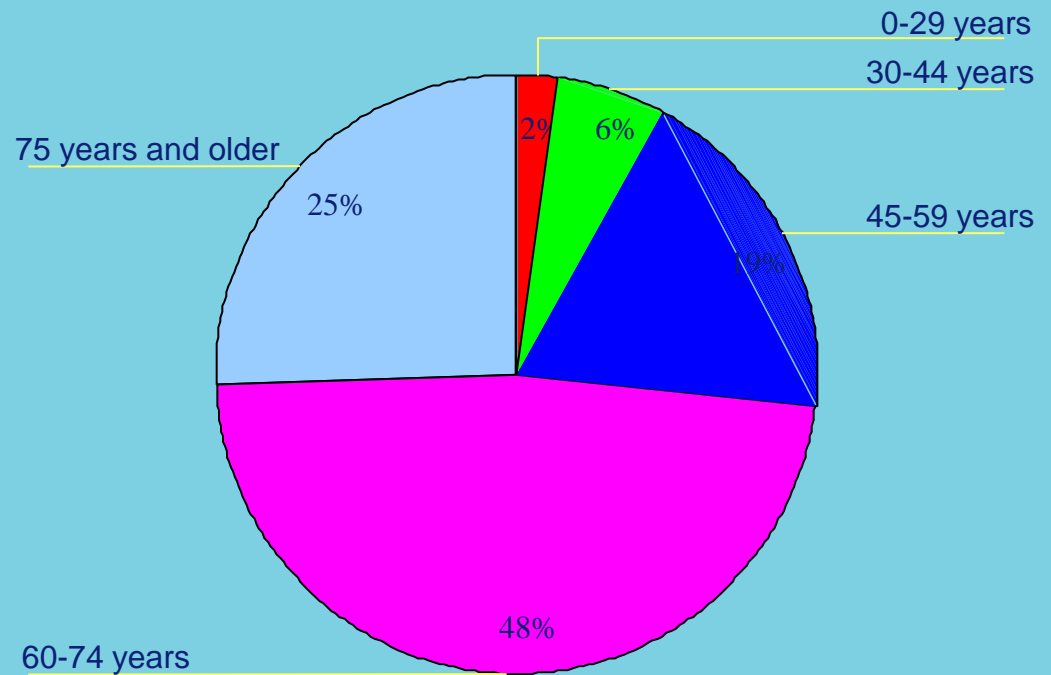
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- The highest prevalence of this tumor is in Asia and Africa, although during the last decades the prevalence in **Western countries in Europe and USA is rising** and **Eastern countries are declining**



Hepatocellular carcinoma in a low-endemic area: rising incidence and improved survival

Caroline D.M. Witjes^a, Henrike E. Karim-Kos^b, Otto Visser^e,
Sanne A.W. van den Akker^b, Esther de Vries^b, Jan N.M. Ijzermans^a,
Robert A. de Man^c, Jan Willem W. Coebergh^{b,f} and Cornelis Verhoef^d



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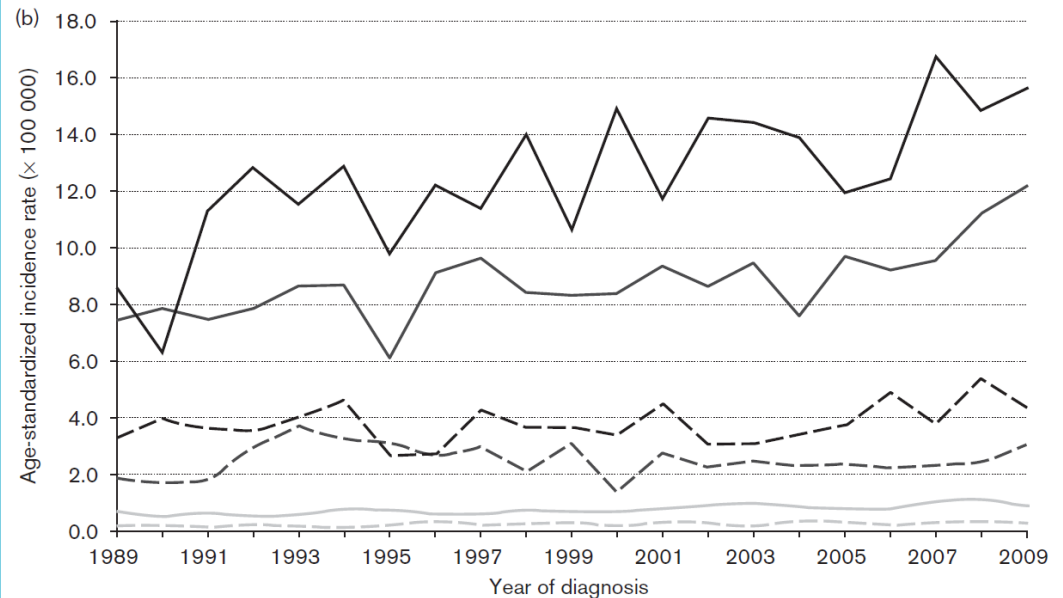
Numbers newly diagnosed per year

Sex	Year	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Men		122	110	131	132	144	160	129	154	159	169	157	173	183	201	216	189	204	203	251	274	277
Women		49	51	47	65	70	66	63	64	72	59	75	46	81	65	59	74	75	73	75	89	87

Sex	EAPC (95% CI)
Men	2.2 (1.6–2.7)*
Women	1.0 (–0.01–2.2)

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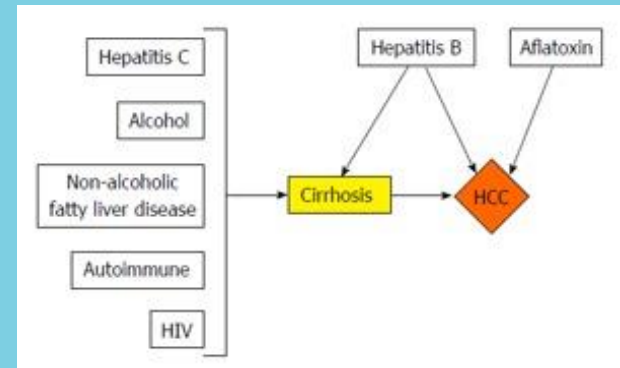
Age (years)	EAPC (95% CI)
Men <60	2.9 (1.8–3.9)*
Men 60–74	1.7 (0.8–2.5)*
Men ≥ 75	2.6 (1.3–3.8)*
Women <60	2.6 (0.3–5.0)*
Women 60–74	0.2 (–1.6–2.1)
Women ≥ 75	0.9 (–0.4–2.3)

Why HCC is Rising?

- Rising incidence of patients with cirrhosis
 - HCV (main reason)
 - HBV
 - Other (NAFLD/Insulin resistance?)
- Improved survival of patients with cirrhosis

Risk factors for HCC

- **Cirrhosis from any cause**
 - HCV
 - HBV
 - Heavy alcohol consumption
 - Non-alcoholic fatty liver disease
- **HBV**
- **Inherited metabolic diseases**
 - Hemochromatosis
 - Alpha-1 antitrypsin deficiency
 - Glycogen storage disease
 - Porphyria cutanea tarda
 - Tyrosinemia
 - Autoimmune hepatitis



Risk factors for HCC

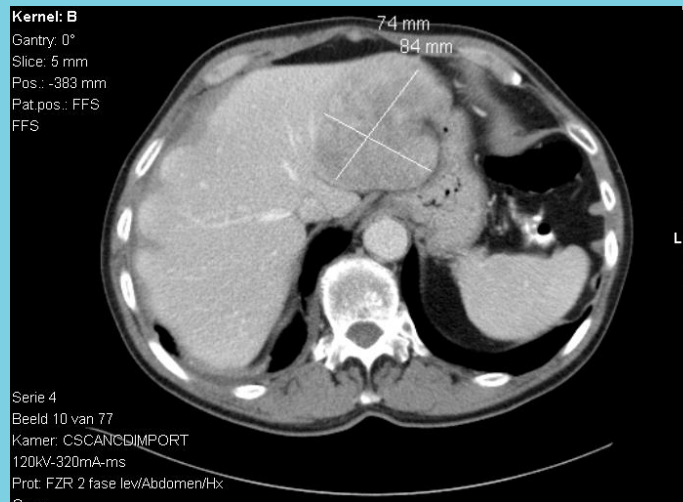
	Hepatitis C	Hepatitis B	Alcohol	Others
Europe	60-70%	10-15%	20%	10%
North America	50-60%	20%	20%	>10%
Asia and Africa	20%	70%	10%	<10%

- HCC is the **sixth** most common neoplasm and the **third** leading cause of cancer-related death in the world
- HCC results in between **250,000 and one million deaths** globally per annum
- **Almost 80% cases have underlying liver cirrhosis** (chronic HBV or HCV infection) and consequently **20% HCC develops in non-cirrhotic livers**
- Compensated cirrhosis have a **3-4% annual incidence of HCC**, and those with chronic hepatitis have an approximate annual risk of **1%**

Hepatocellular Carcinoma

In the non-cirrhotic liver

Abdominal complaints



Hepatocellular Carcinoma

In the non-cirrhotic liver



Hepatocellular carcinoma in cirrhotic versus noncirrhotic livers: results from a large cohort in the Netherlands

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- 1221 cases with HCC in 5 large centers in the Netherlands (2005-2012)

Hepatocellular Carcinoma

In the non-cirrhotic liver

- Non cirrhotic;
- **(A)** histology without cirrhosis either in biopsy or resection specimen in combination with absence of radiological features of cirrhosis.
- **(B)** (in absence of liver histology) all three of the following criteria:
- (1) an aspartate aminotransferase to platelet ratio index less than or equal to 1, (2) two of the following three laboratory tests within normal range: (a) albumin greater than 35 g/l, (b) platelet counts greater than $200 \times 10^9/l$, (c) international normalized ratio less than 1.1, and (3) absence of radiological features of cirrhosis.

Hepatocellular Carcinoma

In the non-cirrhotic liver

Table 1. Patient characteristics of 1221 cases with hepatocellular carcinoma subdivided according to presence or absence of cirrhosis

	Total group	Cirrhosis	No cirrhosis	P-value ^a
Patient number	1221 (100)	983 (81)	238 (19)	
Male sex	936 (77)	779 (79)	157 (66)	< 0.001
Age at HCC diagnosis	63 (8–91)	63 (8–91)	65 (11–88)	0.514
BMI [mean (SD)]	26.7 (5.0)	27.1 (5.0)	25.4 (4.7)	< 0.001
Etiology				< 0.001
Alcohol	349 (29)	312 (32)	37 (16)	
Chronic viral hepatitis				
HBV	197 (16)	162 (16)	35 (15)	
HCV	249 (20)	236 (24)	13 (6)	
Coinfection	19 (2)	18 (2)	1 (< 1)	
Hemochromatosis	37 (3)	29 (3)	8 (3)	
NAFLD	181 (15)	114 (12)	67 (28)	
Others	43 (3)	39 (4)	4 (2)	
No risk factors known	146 (12)	73 (7)	73 (30)	
ALT (U/l)	47 (4–1193)	49 (4–1193)	39 (8–712)	< 0.001
AST (U/l)	66 (14–8678)	71 (15–8678)	46 (14–1344)	< 0.001
Albumin	38 (13–62)	37 (13–58)	43 (16–62)	< 0.001
Platelets	146 (8–985)	125 (8–985)	259 (62–724)	< 0.001
INR	1.1 (0.8–2.9)	1.2 (0.8–2.9)	1.0 (0.8–1.8)	< 0.001
PT	13.9 (9.7–36.7)	14.3 (10.0–36.2)	12.3 (9.7–36.7)	< 0.001
APRI	1.6 (0.1–304)	2.0 (0.1–304)	0.6 (0.1–32)	< 0.001
MELD score	9 (6–33)	10 (6–33)	7 (6–29)	< 0.001

Hepatocellular Carcinoma

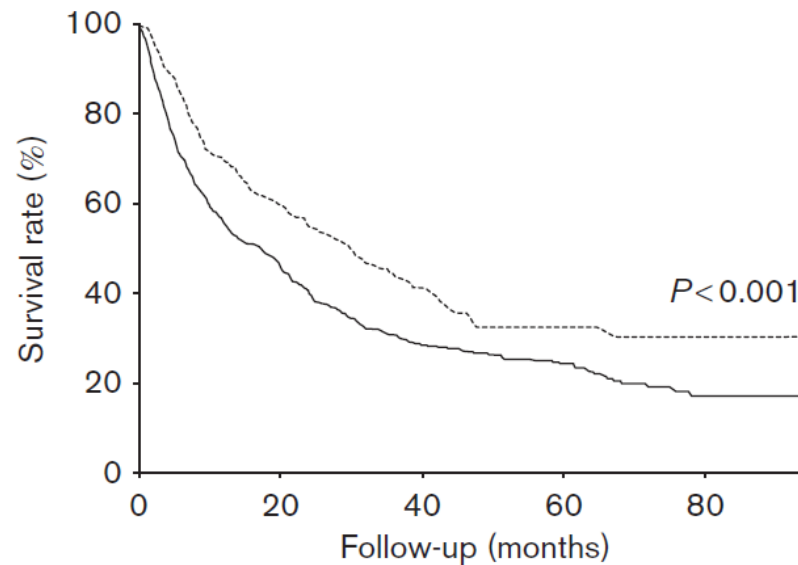
In the non-cirrhotic liver

Table 3. Tumor characteristics of 1221 patients with hepatocellular carcinoma subdivided according to presence or absence of cirrhosis

	Total group	Cirrhosis	No cirrhosis	P-value ^a
Patient number	1221 (100)	983 (81)	238 (19)	
Number of lesions				< 0.001
1	632 (52)	473 (48)	159 (67)	
2	152 (12)	132 (14)	20 (8)	
3	68 (6)	63 (6)	5 (2)	
Multifocal/diffuse	369 (30)	315 (32)	54 (23)	
Tumor size (cm)	5 (1–26)	4 (1–26)	8 (1–26)	< 0.001
BCLC stage				< 0.001
0	75 (6)	72 (7)	3 (1)	
A	345 (28)	301 (31)	44 (18)	
B	406 (33)	274 (28)	132 (56)	
C	299 (25)	247 (25)	52 (22)	
D	96 (8)	89 (9)	7 (3)	
α-Fetoprotein (μg/l)	29 (1–2.7 × 10 ⁶)	35 (1–1.8 × 10 ⁶)	10 (1–2.7 × 10 ⁶)	< 0.001
Treatments				< 0.001
Surgical therapy	341 (28)	215 (22)	126 (53)	
Resection	214 (18)	95 (10)	119 (50)	
Transplantation	120 (10)	116 (12)	4 (2)	
Both	6 (< 1)	4 (< 1)	2 (1)	
RFA ^b	149 (12)	145 (15)	4 (2)	
TACE/TARE ^c	207 (17)	176 (18)	31 (13)	
Systemic therapy	118 (10)	85 (8)	33 (14)	
Best supportive care	351 (29)	314 (32)	36 (15)	
Unknown	55 (4)	48 (5)	8 (3)	

Hepatocellular Carcinoma

In the non-cirrhotic liver



Number at risk					
Cirrhosis	919	310	129	63	15
No cirrhosis	229	99	47	24	6

Fig. 1. Observed survival of patients with hepatocellular carcinoma in the 'cirrhosis' group (solid line) and 'no cirrhosis' group (dotted line) (Kaplan-Meier survival curve; log-rank $P < 0.001$).

Hepatocellular Carcinoma

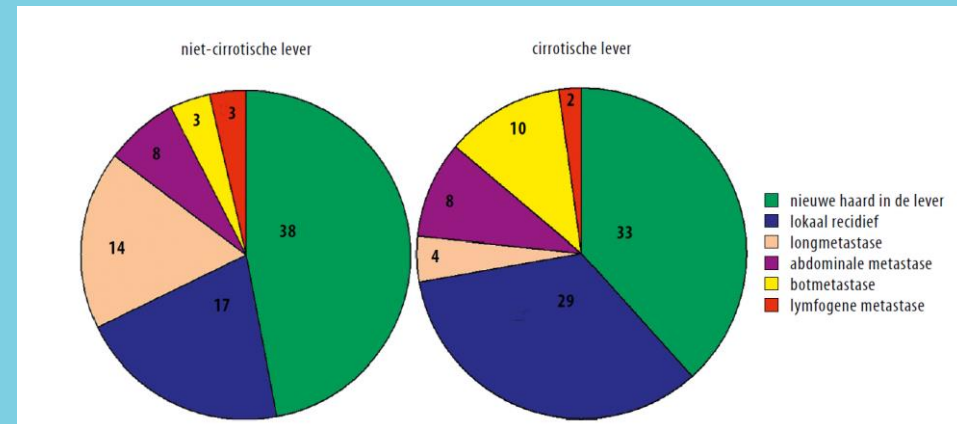
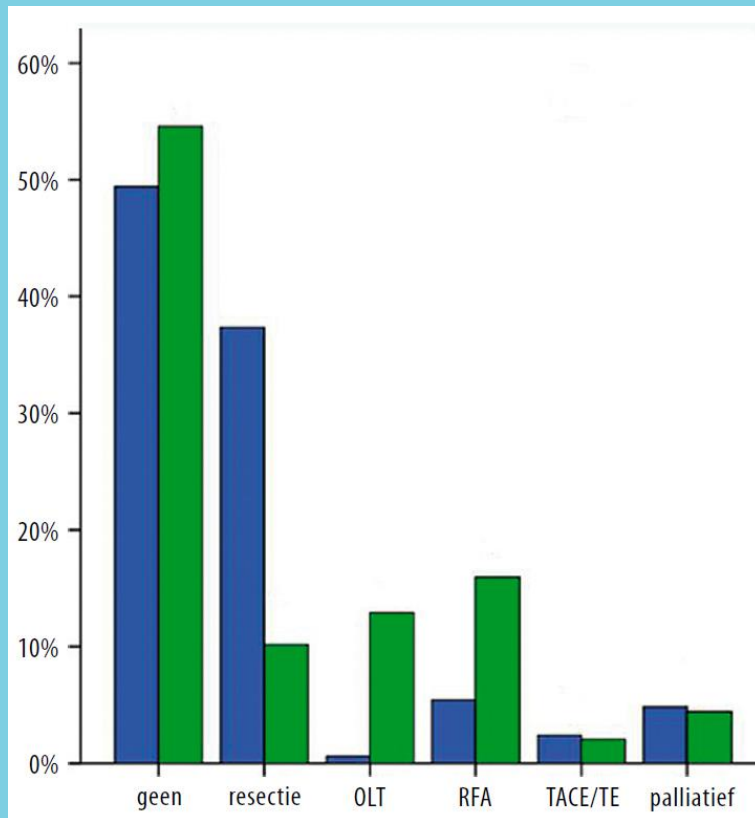
In the non-cirrhotic liver

- ***Survival;***
- In patients who received *TACE* or *Sorafenib* treatment, survival was not different between cirrhotic and non-cirrhotic patients.
- In patients who received *Surgical Treatment*, survival was significantly different between cirrhotic and non-cirrhotic patients.

Hepatocellular Carcinoma

In the non-cirrhotic liver

- Erasmus MC in 461 pts (2000-2007);



Recurrence percentages, and locations are equal.

Recurrence treatment percentages significant different.

Hepatocellular carcinoma in a low-endemic area: rising incidence and improved survival

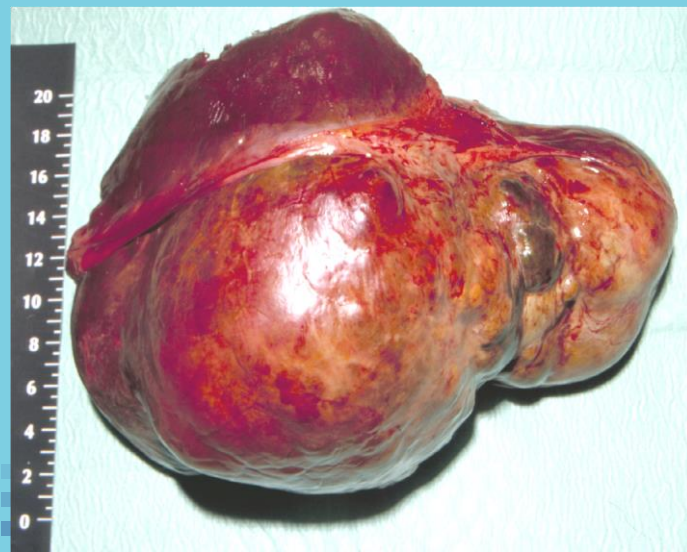
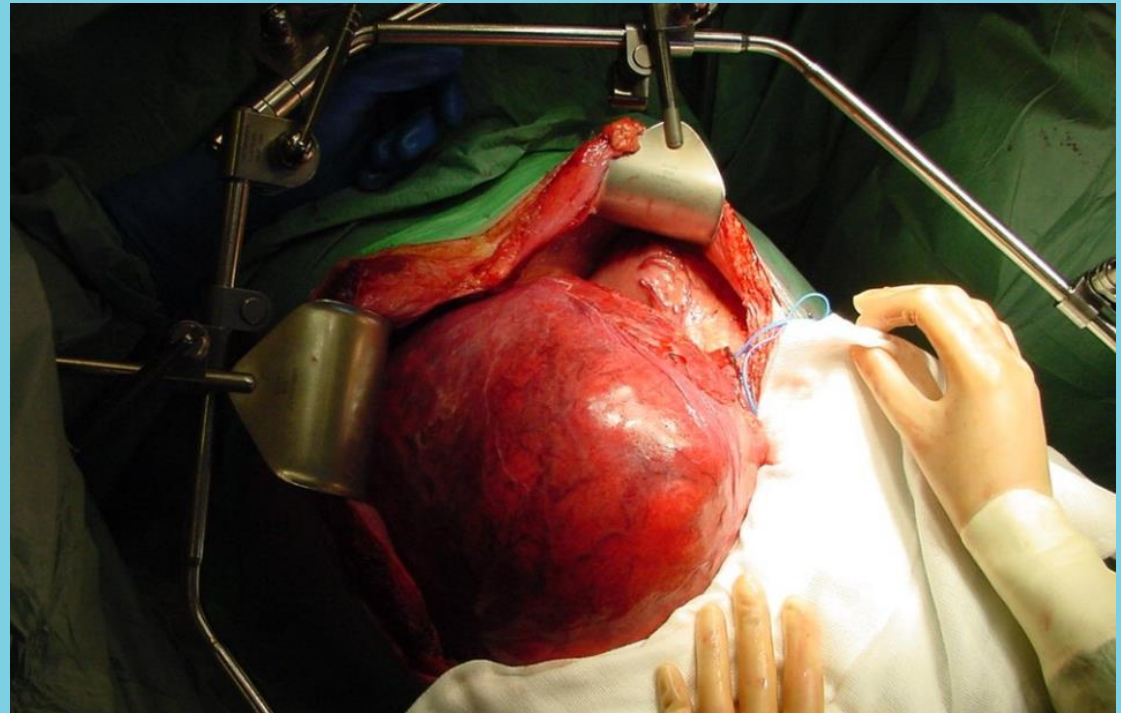
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Table 1 Time trends of treatment patterns for patients with hepatocellular carcinoma in the Netherlands during the period 1989–2009

Therapy	Period of diagnosis ^a			
	1989–1994 <i>n</i> (%)	1995–1999 <i>n</i> (%)	2000–2004 <i>n</i> (%)	2005–2009 <i>n</i> (%)
Surgery	102 (9)	136 (12)	194 (15)	372 (23)
Chemotherapy/ irradiation	65 (6)	47 (4)	66 (5)	172 (11)
Other/no therapy	980 (85)	918 (83)	1027 (80)	1064 (66)
Total	1147	1101	1287	1608

Hepatocellular Carcinoma

In the non-cirrhotic liver



Hepatocellular Carcinoma

In the non-cirrhotic liver

Outcomes of hepatectomy for noncirrhotic hepatocellular carcinoma.

Reference	Major resection n, (%)	Morbidity n, (%)	Mortality n, (%)	Overall survival (%)			Disease-free survival (%)		
				1 year	3 years	5 years	1 year	3 years	5 years
Eastern countries									
Sasaki	26 (54.1)	–	0 (0)	94.0	84.0	68.0	79.0	58.0	54.0
Poon	124 (80)	60 (39.0)	7 (4.5)	79.7	58.7	45.6	57.2	41.9	35.0
Shimada	37 (56.9)	16 (24.6)	1 (1.5)	88.0	75.3	63.0	83.0	54.0	38.0
Nagasue	47 (47.0)	22 (22)	3 (3.0)	97.0	76.0	50.0	79.0	38.0	31.0
Chen	179 (70.4)	–	12 (4.8)	61.9	46.0	35.9	48.7	31.0	24.0
Chang	106 (47.5)	–	3 (1.3)	–	–	53.0	–	–	36.8
Taura	48 (38.0)	40 (32.0)	2 (2.0)	–	–	81.0	–	–	–
Xu	6 (6.2)	8 (8.3)	0 (0)	84.4	62.5	47.9	56.3	39.6	33.3
Kim	148 (32.6)	–	3 (0.7)	92.4	81.7	73.3	72.0	61.0	53.3
Zhou	65 (35.5)	51 (27.8)	1 (0.5)	93.4	65.3	45.6	87.9	57.8	42.9
Western countries									
Bismuth	49 (72.0)	13 (19.0)	2 (2.9)	74.4	51.6	40.2	70.5	42.8	33.4
Grazi	–	35 (25.9)	4 (3.0)	84.0	67.9	51.0	77.6	58.0	45.6
Verhoef	18 (81.8)	–	0 (0)	96.0	68.0	68.0	86.0	–	56.0
Dupont-Bierre	51 (60.7)	22 (26.2)	3 (3.6)	77.8	55.0	44.4	–	–	–
Laurent	66 (35.0)	25 (23.0)	7 (6.5)	–	55.0	43.0	–	43.0	29.0
Bège	72 (64.3)	36 (31.0)	7 (6.0)	72.0	54.0	40.0	60.0	40.0	33.0
Lang	54 (67.5)	19 (24.0)	6 (6.3)	77.0	48.0	30.0	–	–	–
Lubrano	11 (55.0)	2 (10.0)	1 (5.0)	85.0	70.0	64.0	84.0	66.0	58.0
Rayya	41 (74.5)	–	–	69.0	48.0	48.0	–	–	–
Smoot	91 (63.6)	47 (32.9)	5 (3.5)	84.6	51.0	38.4	–	–	–
Shrager	103 (50.0)	–	6 (2.9)	79.1	60.3	46.3	–	–	–
Truanti	52 (58.4)	25 (28.1)	5 (5.6)	–	–	61.4	–	–	58.4
Young	59 (72.8)	28 (34.5)	3 (3.7)	80.0	62.0	60.0	70.0	58.0	51.0
Faber	26 (57.7)	25 (55.5)	0 (0)	94.0	64.0	26.0	–	–	–
Beard	63 (48.1)	–	4 (3.0)	93.8	–	72.9	85.4	–	56.7
Chiche	–	56 (37.8)	7 (4.7)	75.4	54.7	38.9	60.3	38.0	29.1
Thelen	67 (60.9)	34 (30.9)	5 (4.5)	77.7	60.0	46.6	69.0	53.0	42.0
Witjes	29 (72.5)	15 (37.5)	0 (0)	95.0	60.0	51.0	–	–	–
Arnaoutakis	90 (28.2)	–	11 (3.4)	86.9	68.9	54.5	71.1	45.0	35.0
Other countries									
Ardiles	38 (74.5)	22 (43.0)	0 (0)	90.0	67.0	–	65.0	37.0	–
Bhaijee	9 (56.2)	5 (31.0)	0 (0)	100.0	56.0	38.0	–	–	–

Hepatocellular Carcinoma

In the non-cirrhotic liver

Size of the tumour is not a drawback for resection.

Size of the tumour is not a prognostic factor.

Consider resection if a recurrence is detected.

Five-year survival rate > 50%

Hepatocellular Carcinoma

In the non-cirrhotic liver

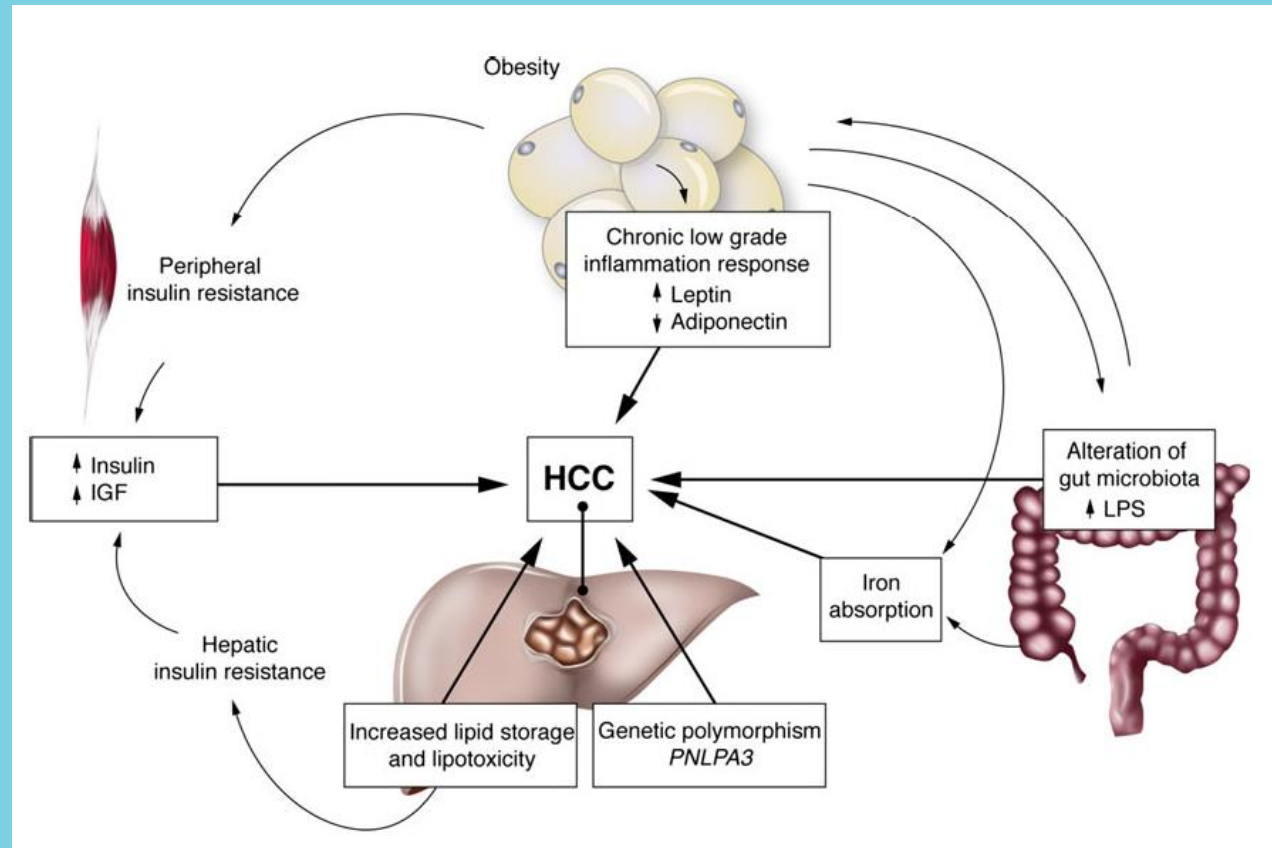
- ***Conclusions;***

- Presence of HCC without cirrhosis was strongly associated with absence of risk factors for underlying liver disease, presence of NAFLD, and female sex.
- In absence of cirrhosis, resections were more often performed, despite larger tumor size.
- Survival in non-cirrhotic patients was significantly better compared with those with liver cirrhosis, probably by more surgical interventions.
- Size does not matter!

Hepatocellular Carcinoma

In the non-cirrhotic liver

- *The Story of HCC in NAFLD*



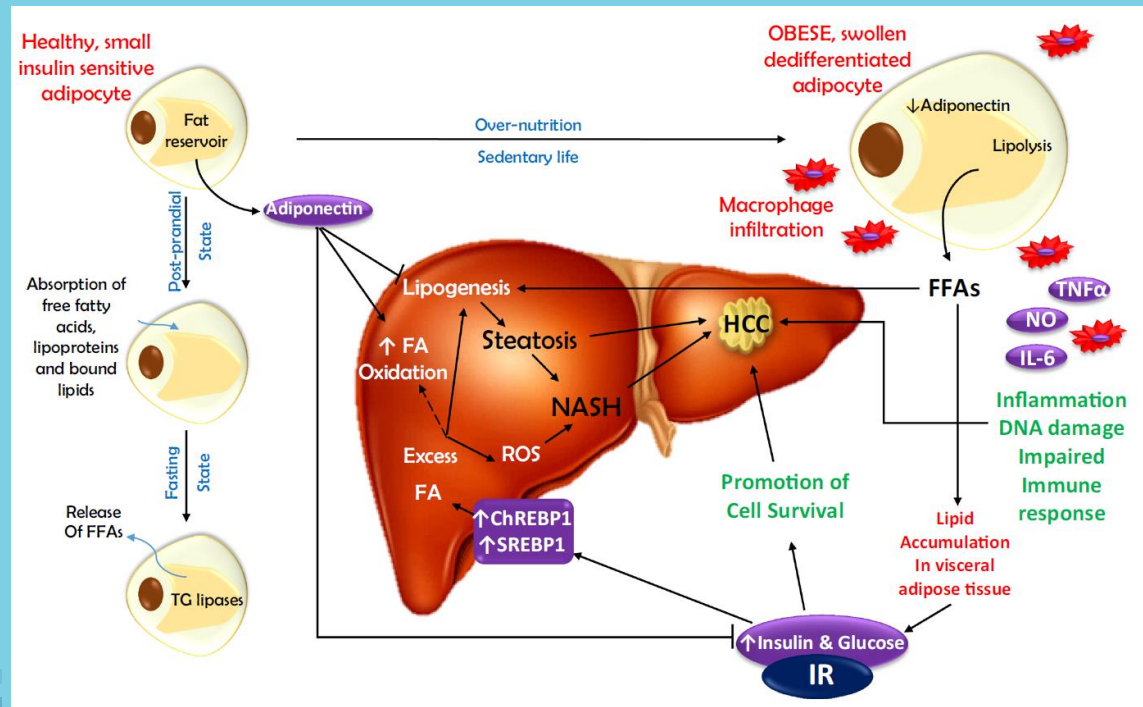
Hepatocellular Carcinoma

In the non-cirrhotic liver

REVIEW

Hepatocellular Carcinoma in Obesity, Type 2 Diabetes, and NAFLD

Helen L. Reeves¹ · Marco Y. W. Zaki¹ · Christopher P. Day²



Hepatocellular Carcinoma

In the non-cirrhotic liver

- ***Special one; Fibrolamellar HCC***
- Thought to be a **rare variant** of conventional hepatocellular carcinoma (HCC), accounting for 0.85 to 16 % of all hepatocellular carcinomas.
- It occurs in a distinctly different group of patients which are **young** and usually **not in the setting of chronic liver disease**

Hepatocellular Carcinoma

In the non-cirrhotic liver

- **Special one; Fibrolamellar HCC**

Table 1 Clinicopathologic characteristic of fibrolamellar hepatocellular carcinoma in comparison to conventional hepatocellular carcinoma

Characteristic	FL-HCC	HCC	Comments
Age at presentation	Young	Older	
Sex predilection	No	4-8 times more often in men	
Distinct geographic distribution	No	Yes	HCC is more often seen in Africa and Asia
Distribution of lesions	Mostly solitary	Mostly multiple	
Growth pattern	Indolent	Aggressive	
Stage at diagnosis	Mostly advanced	Mostly advanced	Despite the advanced stage at diagnosis, prognosis is in favor of FL-HCC patients
Chronic viral infection	Absent	Present	
Liver cirrhosis	Absent	Present	Occasionally, underlying liver disease may be present in patients with FL-HCC. If present, incidental and not causative for FL-HCC
α -fetoprotein	Within normal range	Mostly elevated	
Liver resection	Treatment of choice	Not standard	Limited indication in HCC due to cirrhosis
Liver transplantation	Not standard	Curative treatment	If requirements for LT are fulfilled
Prognosis	Favorable	Mostly dismal	No difference in non-cirrhotic patients
Macro-finding	Well-circumscribed, often lobulated mass, a central gray and white scar	Single or massive, multifocal or nodular, and diffuse. Due to lack of stroma in the tumor, often necrosis and hemorrhage	
Histology	Eosinophilic polygonal-shaped cells separated by lamellar fibrosis. A fairly uniform cell pattern. Overall, greater differentiation than HCC	Thickened plates of hepatocytes with eosinophilic or clear cytoplasm. Cells are often arranged in trabecular, pseudoglandular, or solid pattern	Histologic appearances are the most objective and widely accepted differences between FL-HCC and HCC

FL-HCC fibrolamellar hepatocellular carcinoma, HCC conventional hepatocellular carcinoma

Hepatocellular Carcinoma

In the non-cirrhotic liver

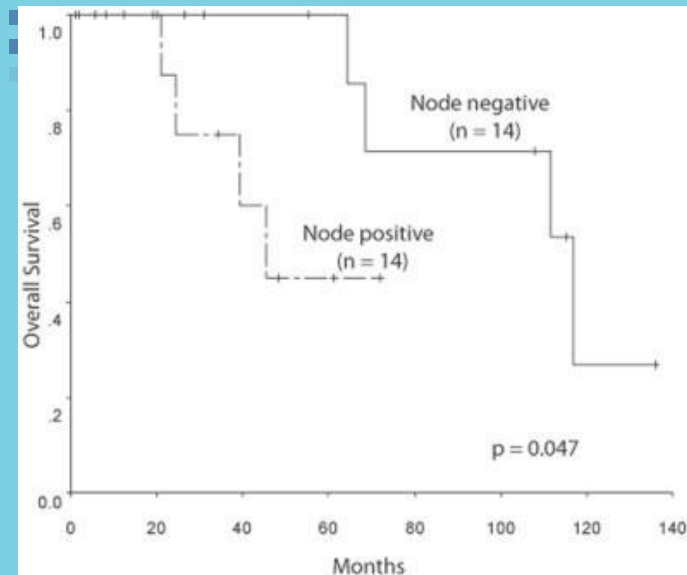
Special one; Fibrolamellar HCC

Young patients (+/- 30 years)

No elevated AFP (<5%)

No gender predominance

30-50% Nodal metastases



Published Series on FL-HCC

Author, Yr	N	Age ^a	Male: female	Cirrhosis/hep B/hep C	AFP elevated	Median size	> 1 tumor	Positive nodes	Vascular invasion	Initial operation	Repeat operation	Median f/u	5-yr survival	Prognostic factors
Ringe, 1992 ¹⁴	20	23	55:45	0/10%/10%	0%	12	45%	45%	30%	Phx 70% OLT 30%	NR	NR	37%	> 1 tumor positive nodes
Hemming, 1997 ¹⁵	10	31	50:50	NR	10%	8	20%	20%	NR	Phx 100%	50%	101	70%	NR
Pinna, 1997 ⁵	41	30	56:44	7%/0%/16%	10%	13	27%	34%	76%	Phx 68% OLT 32%	22%	58	66%	Vascular invasion
El-Gazzaz, 2000 ²⁵	20	27	65:35	0% hep B	0%	14	20%	30%	55%	Phx 55% OLT 45%	NR	25	50%	None
Current series	28	28	43:57	0%/0%/0%	7%	9	11%	50%	36%	Phx 100%	61%	34	56%	positive nodes

hep: hepatitis; AFP: alpha-fetoprotein elevated > 200 ng/mL; Phx: partial hepatectomy; OLT: orthotopic liver transplantation; NR: not reported. ^amean or median.

Hepatocellular Carcinoma

In the non-cirrhotic liver

- **Special one; Fibrolamellar HCC**

Table 2 Summary of clinicopathologic and outcome data of patients with fibrolamellar carcinoma collected from the literature

Author	TP	YP	Total number of patients	♂:♀	Age	CD %	AFP↑	LR %	LT %	5y-OS % LR	5y-OS % LT	DR %	5y-DSF %	5y-OS %
Craig et al. [8]	1918–1973	1980	23	1:1	26	None	0/6	48	None	nr	na	nr	nr	nr (32)
Nagorney et al. [9]	1950–1982	1985	16	1.3:1	26	None	1/6	75	None	nr	na	75	42	50
Berman et al. [17]	1981–1987	1988	19	2.2:1	25	None	4/15	63	26	nr	nr	59	nr	nr (37)
Wood et al. [51]	1960–1983	1988	15	1:2.8	26	None	3/9	60	None	45	na	nr	nr	45 (32)
Iwatsuki et al. [68]	1980–1989	1991	22	nr	nr	nr	nr	55	45	65	38	nr	nr	nr
Ringe et al. [1]	1974–1988	1992	20	1.2:1	23	None	0/18	70	30	40 (45)	nr (29)	60	29	37 (45)
Pinna et al. [2]	1968–1995	1997	41	1.3:1	30	7	2/19	68	32	75	36	66	33	66 (127)
Epstein et al. [30]	1985–1990	1999	17	1:1	24	None	0/16	None	None	na	na	nr	na	nr (14)
El-Gazzaz et al. [3]	1985–1998	2000	20	1:1.9	27	None	0/20	55	45	65	50	45	50	50 (62)
Ichikawa et al. [14]	1989–1997	2000	40	1:1.2	29	None	3/40	62	10	nr	nr	71	nr	nr
El-Serag and Davila [4]	1986–2000	2004	68	1:1	33	nr	nr	nr	nr	nr	nr	nr	nr	37
Kakar et al. [10]	1987–2000	2005	20	1:1	27	None	3/13	nr	nr	nr	nr	nr	nr	45
Moreno-Luna et al. [5]	1990–2003	2005	15	nr	nr	nr	nr	80	None	nr	na	nr	nr	26
Stipa et al. [6]	1986–2003	2006	41	1:1.4	27	None	3/41	68	None	76	na	61	18	76 (112)
Malouf et al. [23]	1987–2007	2012	40	0.3:1	22	3	7/40	100	None	58	na	58	37	58
Mavros et al. [11]	1963–2008	2012	575	1:1.1	21	3	27/266	55	23	70 (222)	34 (32)	33–100	nr	44 (39)
Ang et al. [58]	1986–2011	2013	95	0.7:1	22	nr	3/31	73	4	nr	nr	77	nr	nr
Kaseb et al. [7]	1992–2008	2013	94	1:1	23	6	13/94	59	2	nr	nr	84	nr	46 (57)
Eggert et al. [69]	2000–2010	2013	191	1.7:1	nr	nr	nr	41	46	58	57	nr	nr	34
Groeschl et al. [12]	1993–2010	2014	35	1.7:1	39	14	1/35	100	None	62	na	50	45	62 (174)
Darcy et al. [15]	1981–2011	2015	25	1:1.3	17	None	2/25	84	None	52	na	63	nr	43

Hepatocellular Carcinoma

(In the non-cirrhotic liver)

- ***Take home message;***
- ***Increasing problem in the Western World.***
- ***Increasing number of patients **without viral infection.*****
- ***New disease in **Obesity, DM type II and NAFLD.*****
- ***HCC without underlying liver-disease needs **special attention.*****
- ***New screening indications?***

Questions ?

