Carcinome hépatocellulaire
Actualités 2010/2011

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A prospective study of the rate of progression in compensated, histologically advanced chronic hepatitis C

Dienstag et al., Hepatology 2011

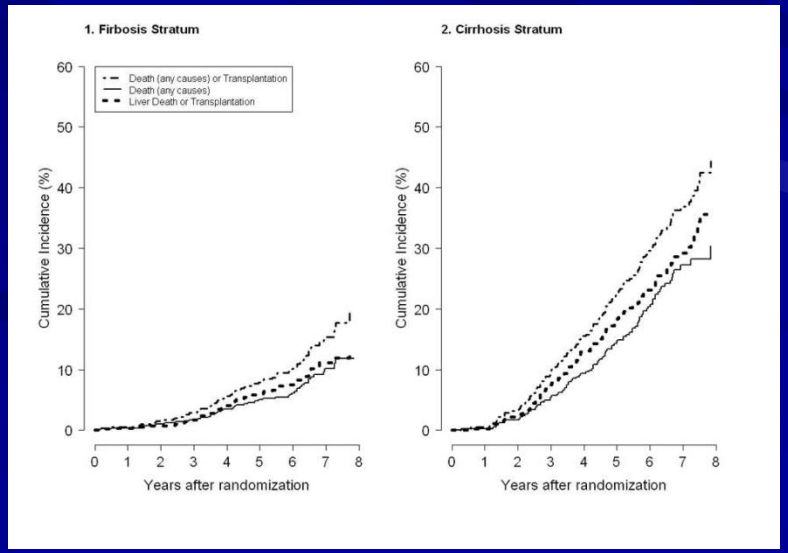
	Fibrose sévère	Cirrhose	p
Stade fibrose %	60	40	
Taux progression F4	10 % / an	-	
Incidence annuelle évenements cliniques (suivi = 4 ans) *	3,3	7,5	0,0001
Incidence annuelle CHC	1,1	2,4	
Décès annuel ou transplantation / 8 ans	2,2	5,3 (10 %/an si CP ≥7)	

n =1050,

HCV (HALTC)

Evènements cliniques :

CP ≥ 7,
CHC
Décès
Ascite



The Incidence and Risk Factors of Hepatocellular Carcinoma in Patients with Nonalcoholic Steatohepatitis

Asha et al., (HEPATOLOGY 2010;51:1972-1978)

HCV (n = 315) vs NASH (n = 195)

TDM + AFP / 6 mois ; suivi median 3.2 ans

	HCV N=315)	NASH (n = 195)	p
Incidence globale	20,3	12,8	0,03
Incidence annuelle	4	2,6	0,09

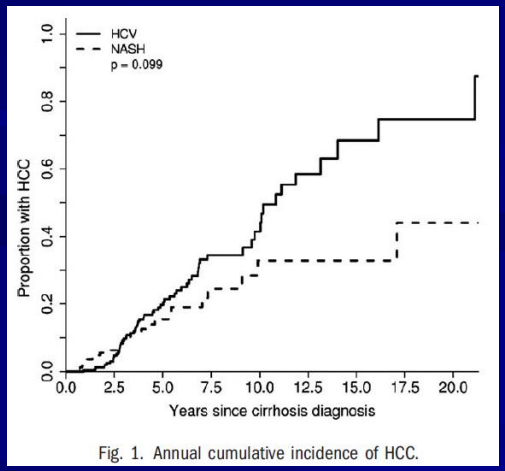


Fig. 1. Annual cumulative incidence of HCC.

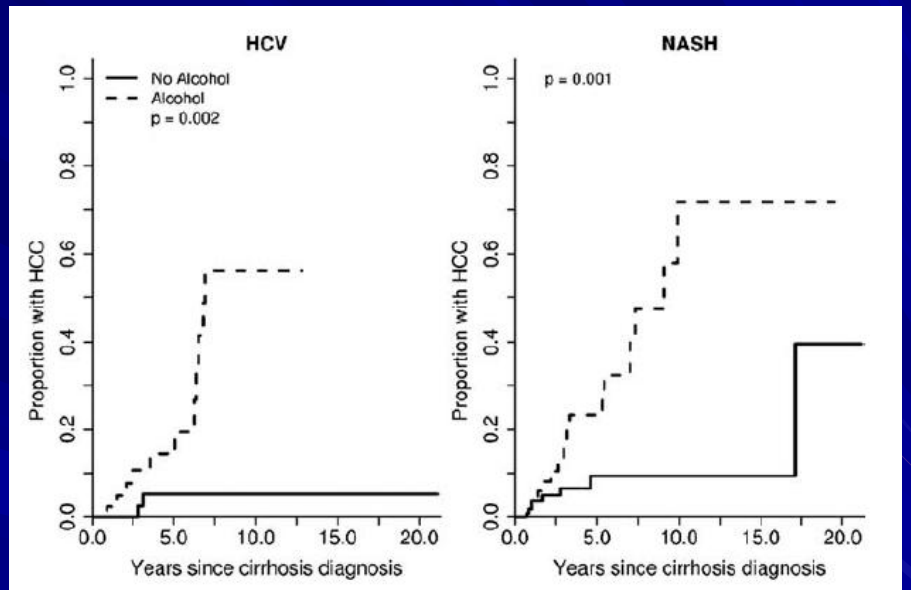


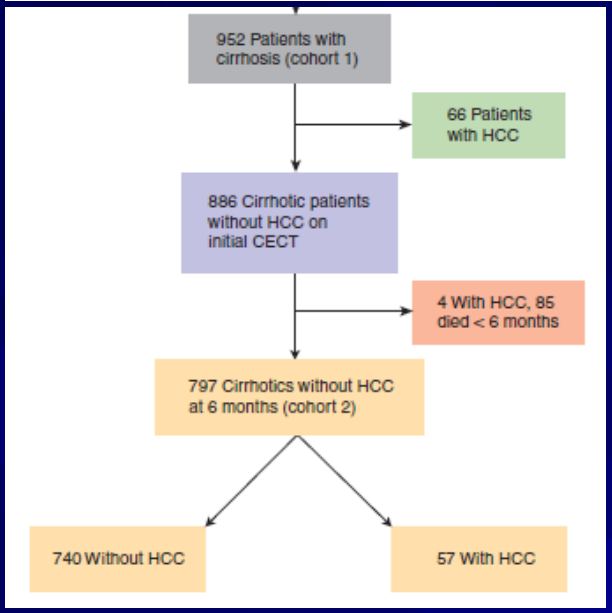
Fig. 3. Social alcohol intake compared with no alcohol intake by disease.

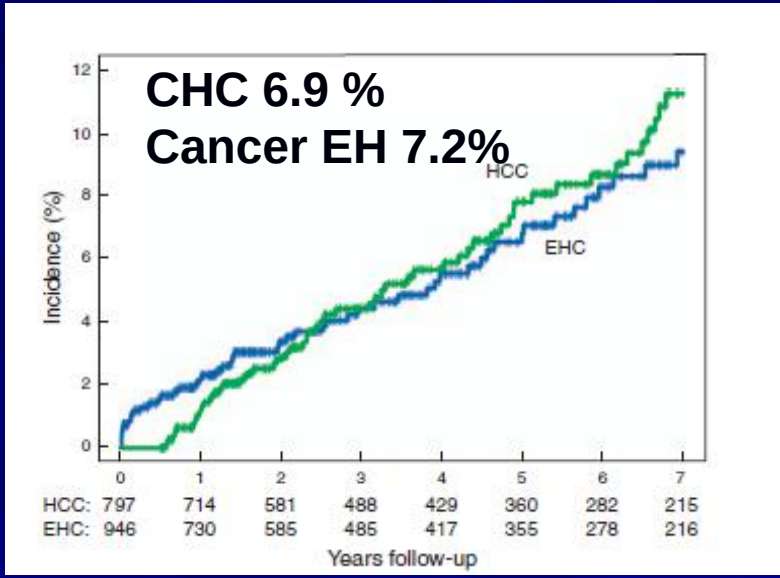
Analyse multivariée : age, alcool

Alcool : HR = 3,5

Hepatic and Extrahepatic Cancer in Cirrhosis: A Longitudinal Cohort Study

Am J Gastroenterol 2011; 106:899–906;





Cohorte rétrospective :TDM/ 6 mois
1997 à 2002
Suivi : 4,7± 3,0 ans

	1an	3 ans	5 ans
Incidence CHC (%)	1,2	4,4	7,8
Incidence CEH (%)	2,2	4,5	6,8

CHC : SIR = 186 (95%, 140-238)
CEH : SIR = 1,83 (95% 1.36-2.36).

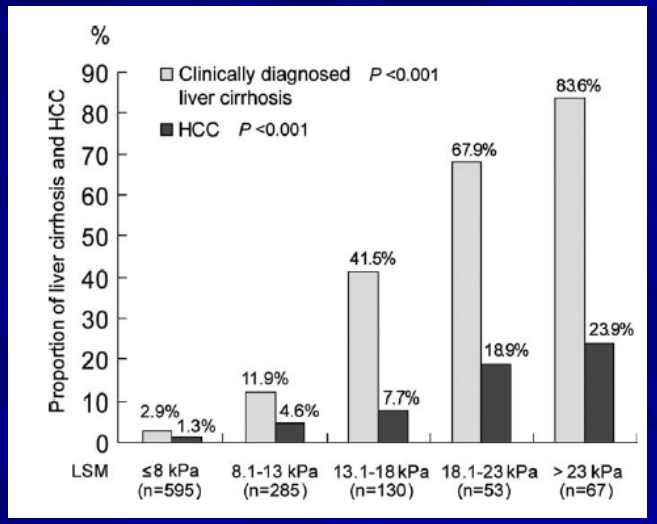
Role de l'alcool dans l'incidence de CEH
(HR 2.73, 95% CI 1.14-4.33)

Risk Assessment of Hepatitis B Virus–Related Hepatocellular Carcinoma Development Using Liver Stiffness Measurement (FibroScan)

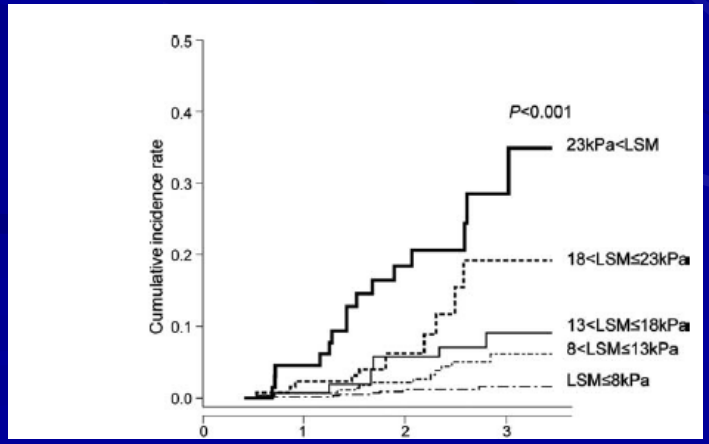
(Hepatology 2011;53:885-894)

N = 1130
Suivi médian : 31 mois

Incidence CHC
1 an : 0,8 %
2 ans : 3,3 %
3 ans : 6 %



Liver stiffness measurement		HR CI 95%	
≤8 kPa		1 (reference)	
8.1-13 kPa	<0.001	3.07 (1.01-9.31)	0.047
13.1-18 kPa	<0.001	4.68 (1.40-15.64)	0.012
18.1-23 kPa	<0.001	5.55 (1.53-20.04)	0.009
>23 kPa	<0.001	6.60 (1.83-23.84)	0.004

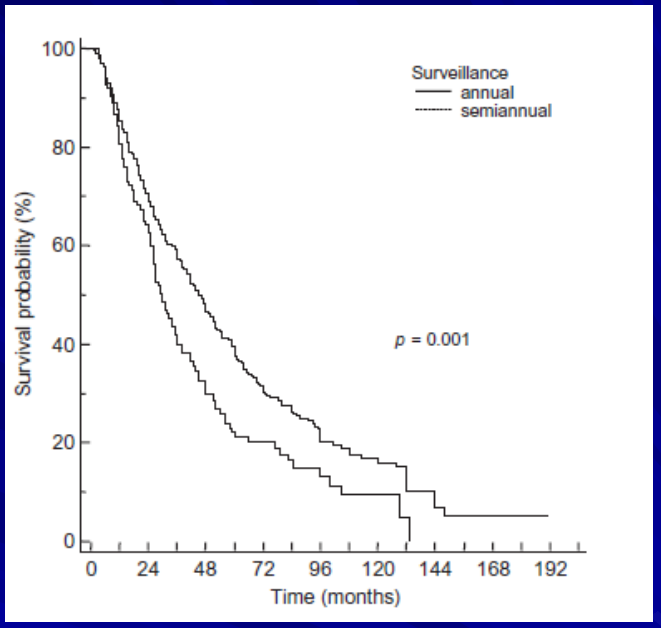


Semiannual surveillance is superior to annual surveillance for the detection of early hepatocellular carcinoma and patient survival

Santi V et al, JH 2010

649 CHC diagnostiqués chez des malades Child-Pugh A ou B

	Dépistage / 6 mois	Dépistage / 1 an	p
Effectifs	510	139	
Sévérité CHC	24	5	< 0,001
- incidence nodule ≤ 20 mm	2,5	3,3	< 0,001
- diamètre médian			
Faisabilité TTT curatif (%)	47,7	43,8	<0,02
Survie observée (mois)	45	30	< 0,001



Survie (an)	1	3	5
Gr. 6 mois	85,4	57,2	37,5
Gr. 1 an	80,6	40,1	21,1

Risque décès Gr.1 an : HR = 1,39

Hepatic Resection Versus Radiofrequency Ablation for Very Early Stage Hepatocellular Carcinoma: A Markov Model Analysis

Cho et al. HEPATOLOGY, Vol. 51, No. 4, 2010

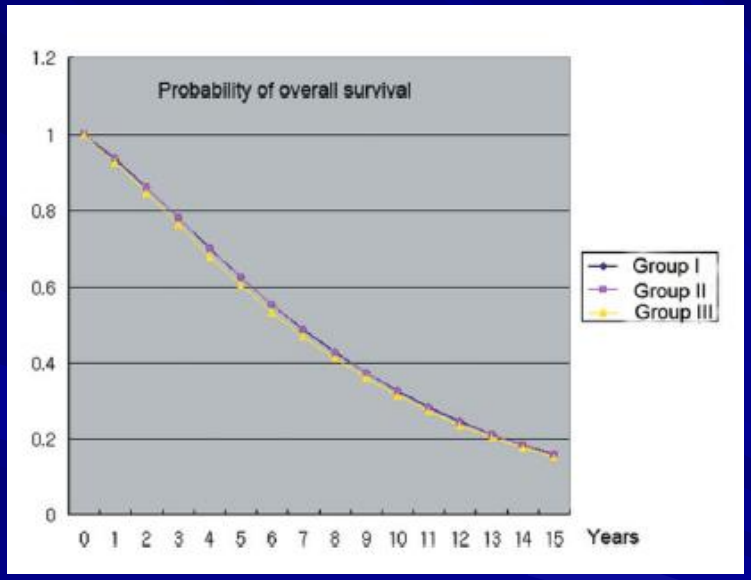
Cohortes virtuelles 10,000 patients

CHC < 20 mm

Résection

RF puis résection

RF seule



Survie attendue à 5 ans

G1 = 62,5 ans

G2 = 62,3 ans

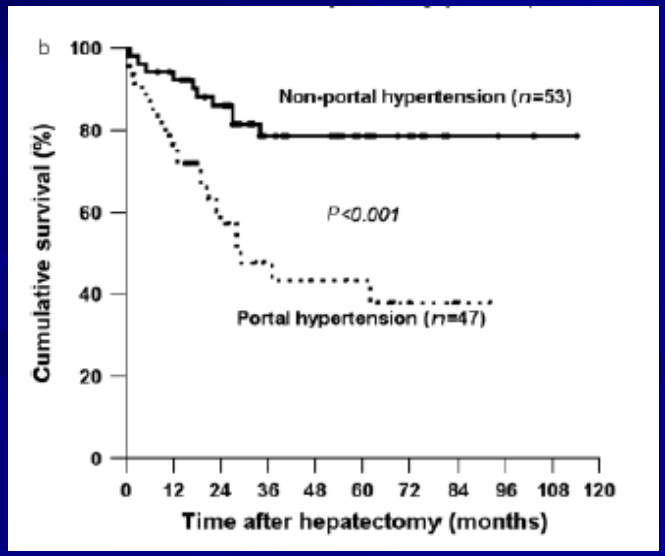
G3 = 60,3 ans

Predictive factors for long-term survival in patients with clinically significant portal hypertension following resection of hepatocellular carcinoma

Choi, Liver Int. 2011;31:485-93

100 patients cirrhotiques CP = A opérés pour un CHC
HTP = VOG, GC, SM ≥ 12cm avec plaquettes < 100 G/l

	HTP – (n = 53)	HTP +(n = 47)	p
Complications hépatiques (%)	15,1	36,2	0,015
Mortalité péri-opératoire (%)	1,9	6,4	NS
Décès « hépatique » (%)	3,8	27,7	0,001
Décès / tumeur (%)	13.2	19.1	NS
Survie 5 ans (%)	78,7	37,9	0,001



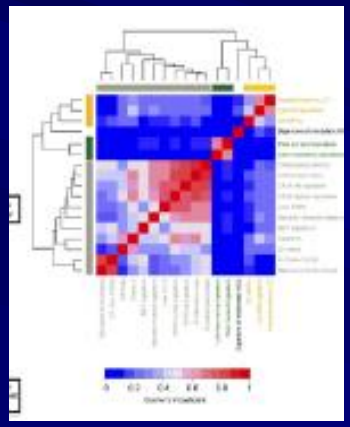
Facteurs indépendants de survie

- **HTP ++**
- **Albumine**
- **Nodules multiples**
- **Invasion vasculaire**

Combining Clinical, Pathology, and Gene Expression Data to Predict Recurrence of Hepatocellular Carcinoma

Villanueva et al GASTROENTEROLOGY 2011;140:1501–1512

Signatures génétiques (G3, “poor survival”) du tissu tumoral et adjacent (cirrhose) prédictives de la récidive



Tissu tumoral : signature G3-proliferation : HR, 1.75; p = 0,003

Tissu adjacent “poor-survival signature” : HR, 1.74; p = 0,004

Prévention secondaire Interféron

Meta-analysis: interferon improves outcomes following ablation or resection of hepatocellular carcinoma

A. K. Singal*, D. H. Freeman Jr† & B. S. Anand‡

Aliment Pharmacol Ther 2010; 32: 851–858

10 études (n = 645, 301)

Prévention CHC OR : 0.26 (0.15-0.45) ; p < 0.00001

Survie à 5 ans (n= 505) : OR = 0,31, 0,21-0,46 ; p < 0,00001

Bénéfice surtout si répondeur virologique

Adjuvant interferon therapy after curative therapy for hepatocellular carcinoma (HCC): A meta-regression approach

Shen et al Journal of Hepatology **2010** vol. 52 | 889–894

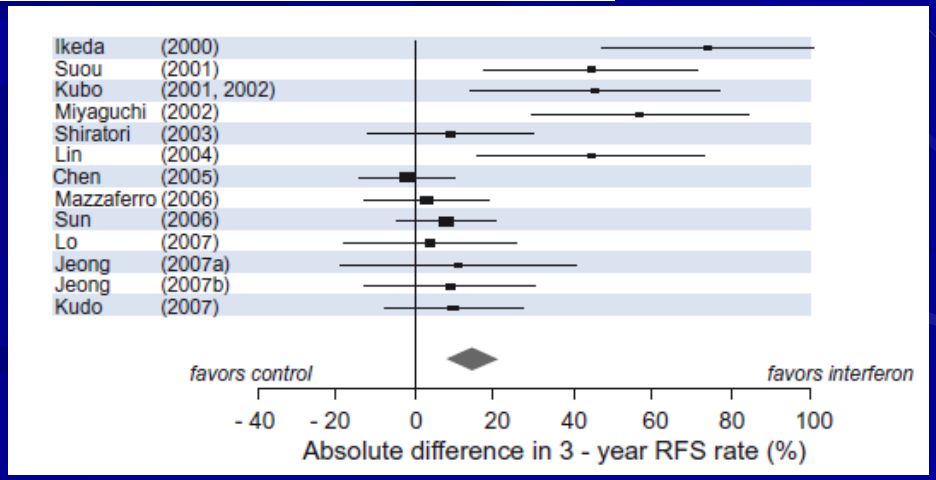
13 études (9 ER, 4 cohortes, n = 1180)

Survie sans récidive (p<0.01)

1 an : 7.8% (3.7-11.8%)

2 ans : 35.4% (30.7-40.0%)

3 ans : 14.0% (8.6-19.4%)



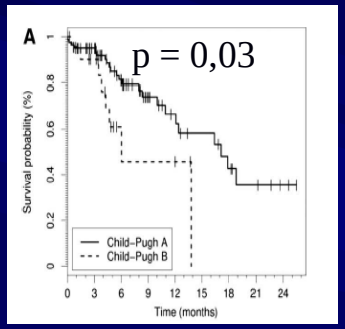
Incidence CHC 3 ans

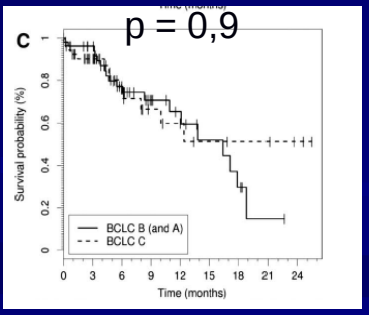
Radioembolization with Yttrium-90 Glass Microspheres in Hepatocellular Carcinoma: European Experience on Safety and Long-Term Survival

(Hepatology 2010;52:1741-1749)

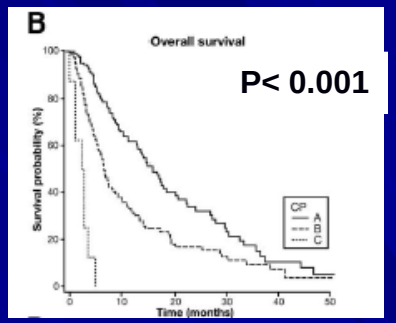
Radioembolization for Hepatocellular Carcinoma Using Yttrium-90 Microspheres: A Comprehensive Report of Long-term Outcomes

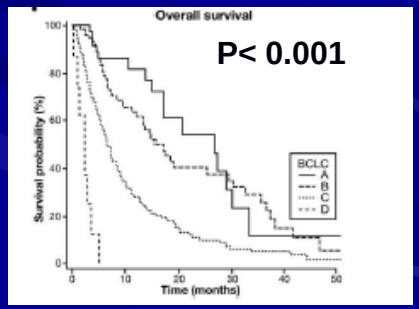
GASTROENTEROLOGY 2010





	Hillgard (HY 2010)	Salem GY 2010
Population	n = 108, CP ≤ 7,	n = 291
Stade CHC (BCLC, %))	B 47, C 54	A 17, B 28, C 52
Réponse complete (%)	3	23
Reponse partielle (%)	37	34
Maladie stable (%)	53	-
Progression (%)	6	-
Temps à progression (mois)	10	7,9
Survie globale (médiane en mois)	16,4	BCLC A : 26,2 BCLC B : 17,2 BCLC C : 7,3





Survival after 90Y resin microsphere radioembolization of hepatocellular carcinoma across BCLC stages: A European evaluation. Sangro et al., HY 2011

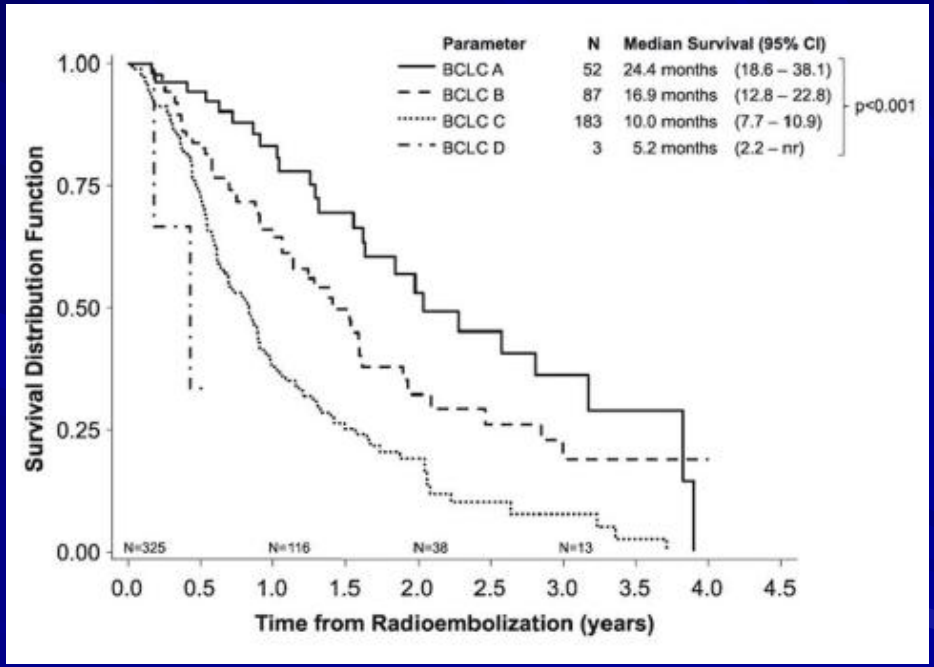
Multicentrique européenne 8 centres, n = 325

78 % cirrhose, CP = A 82%, CLC C: 56 %,BCLC B 27%

Survie globale (médiane)
12.8 months

Facteurs pronostiques :

- ECOG
- Nodules >5
- INR>1.2
- Localisation extrahepatique



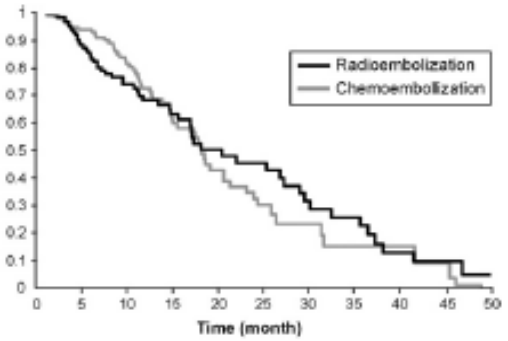
Toxicité : 5.8% of patients : hyper bilirubinémie (≥ grade 3)

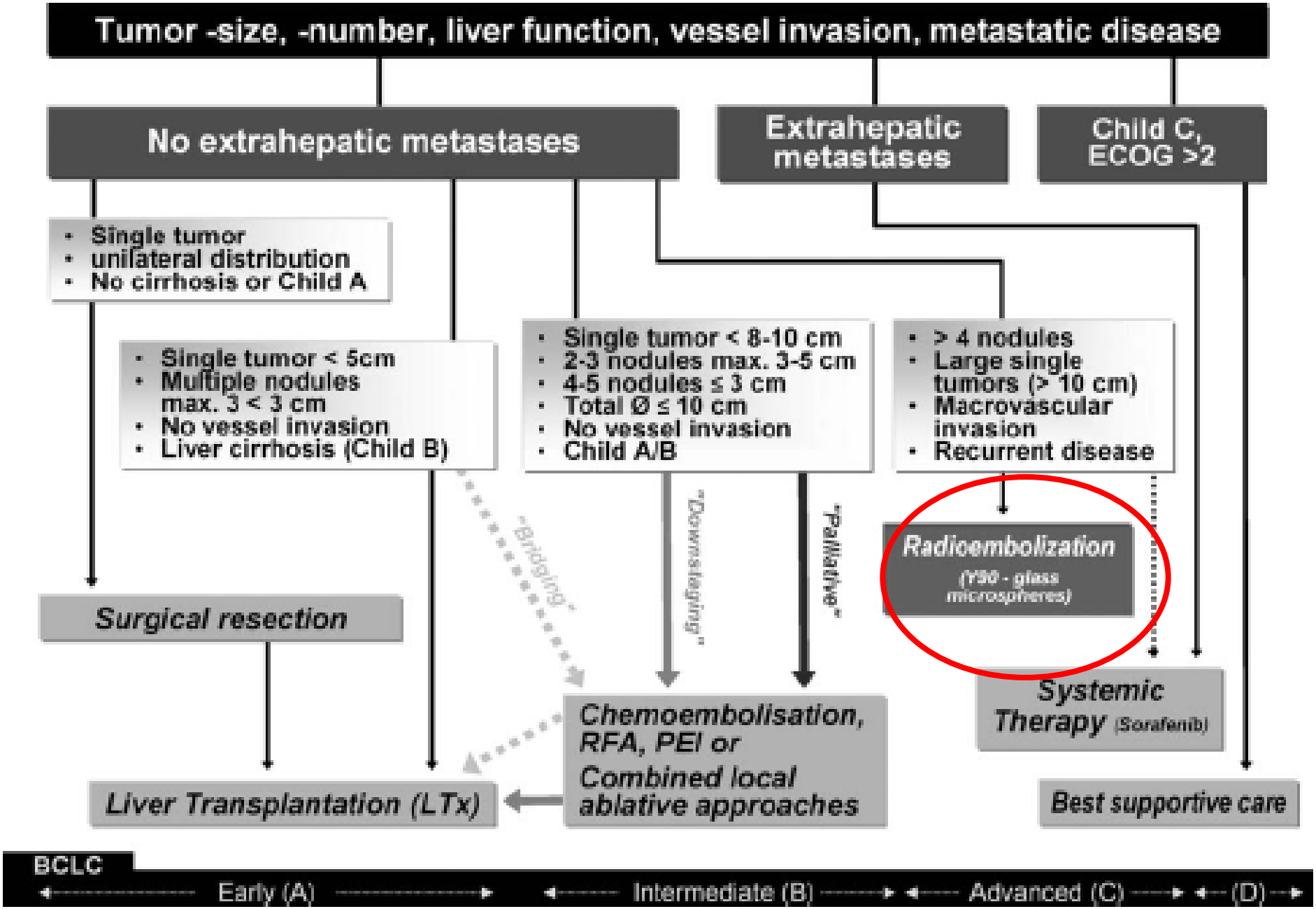
Radioembolization Results in Longer Time-to-Progression and Reduced Toxicity Compared With Chemoembolization in Patients With Hepatocellular Carcinoma

GASTROENTEROLOGY 2011;140:497–507

	CEL	RIST	p
Population	n = 122	n = 123	
Stade CHC (BCLC, %))	A 39 B 50 C 9	A 35, B 53, C 10	
Taux Réponse global (%)	69	72	NS
Temps à réponse (mois)	2,2	1,2	0,01
Temps à progression (médiane, mois)	8,4	13,3	0,05
Survie médiane (mois)	17,4	20,5	NS

Douleur abdominale (p< 0.001) et cytolyse hépatique (p< 0,004) plus fréquentes avec CEL





Hillgard et al , Hepatology 2010;52:1741-1749

Thérapies ciblées : aujourd'hui le futur

Sorafenib
Bevacizumab
Erlotinib
Everolimus
Brivanib…

1ère ligne : 3 essais de phase III

- Erlotinib + Sorafenib vs Sorafenib
- Brivanib vs Sorafenib
- Linifanib vs Sorafenib

2ème ligne : 3 essais

- Everolimus (rapamycine) vs placebo
- Brivanib vs placebo
- Brivanib vs placebo (Asie)

Prévention secondaire

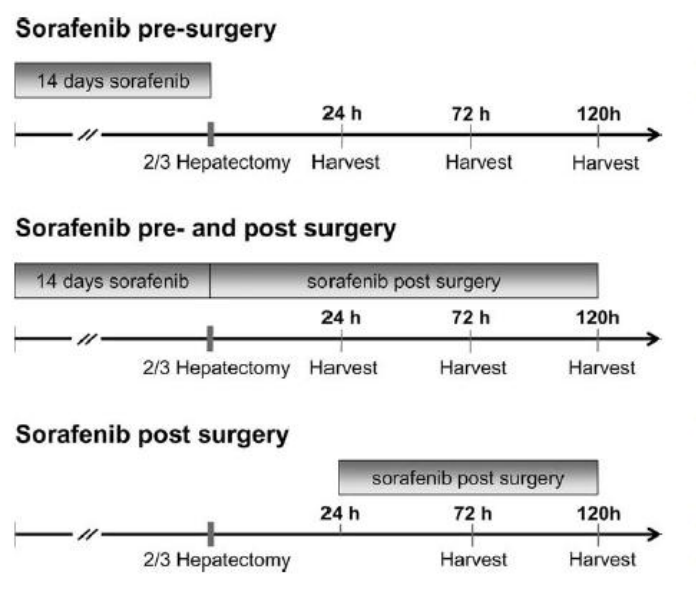
- STORM : Sorafenib vs placebo : BCLC 0/A
- Post-TOH :
  - Rapamycine vs tacrolimus
  - Rapamycine vs Everolimus (mTOR)

Effect of Sorafenib on Murine Liver Regeneration

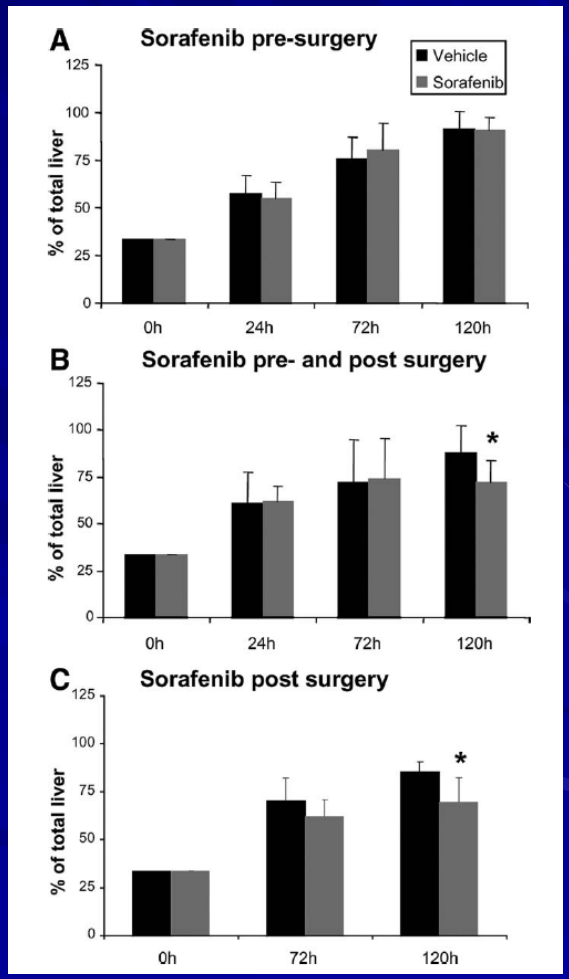
Caroline Hora,[1] Pamela Romanque,[1,2] and Jean-François F. Dufour[1,3]

(HEPATOLOGY 2011;53:577-586)

Administration sorafenib PO 30 mg/kg/day



Evaluation régénération
- % poids initial foie
- prolifération cellulaire



Résultats :

Sorafenib pré-chirurgie : régénération normale

Sorafenib pré/post et post-chirurgie :

- Diminution régénération de 20 % ($p \leq 0,02$)
- Diminution prolifération cellulaire
- Complications de cicatrisation

Prévention CHC

Mc Mahon et al., HY 2011 : Vaccin VHB et éradication

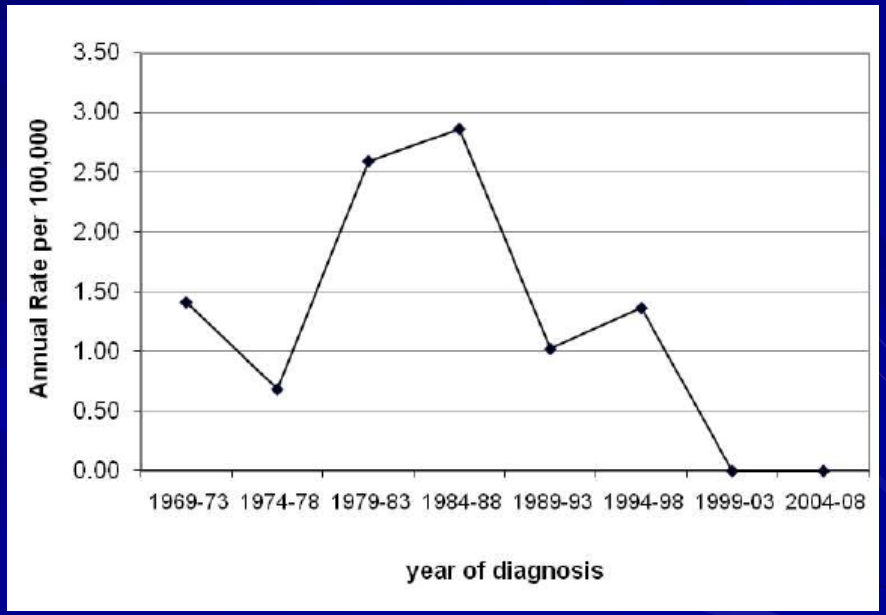
Vaccination universelle nouveaux nés et screening anti Hbs 1984

VHB + : suivi semestriel alpha-fetoprotein depuis 1982

Incidence **hépatite aiguë** < 20 ans :
19/100,000 à 0/100,000 en 10 ans

Incidence **CHC** chez moins de 20 ans :
3/100,000 to zero en 10 ans

Et absence de nouveaux cas depuis 1999



Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: Incidence and survival in hepatitis C patients with advanced fibrosis

Cardoso et al Journal of Hepatology **2010** vol. 52 | 652–657

Hépatite C avec fibrosis sévère (n=127) ou cirrhose (n=180) ; suivi de 3.5 ans (1-18)

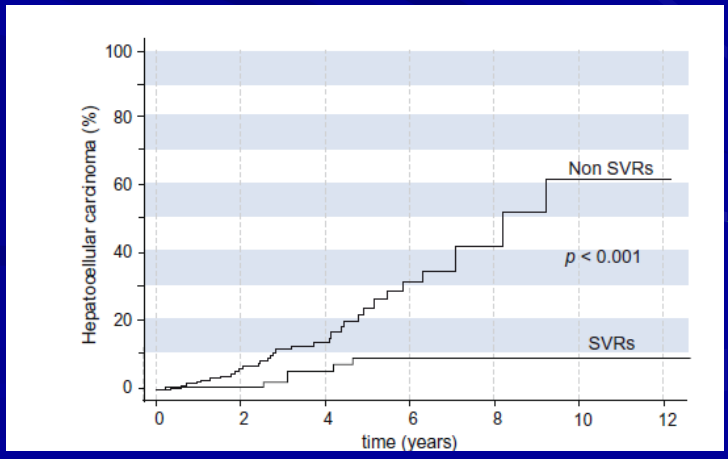
	SVR -	SVR +	p
Incidence CHC (/100 pt-année)	**5,85**	**1,24**	**< 0,001**
Complications hépatiques	**4,16**	**0,62**	**< 0,001**
Décès hépatiques	**3,76**	**0,61**	**< 0,001**

RVS : facteur prédictif

CHC (HR 3.06)

Complications hépatiques (HR 4.73)

Décès (HR 3.71)



Maintenance therapy with peginterferon alfa-2b does not prevent hepatocellular carcinoma in cirrhotic patients with chronic hepatitis C. Bruix Gastroenterology 2011

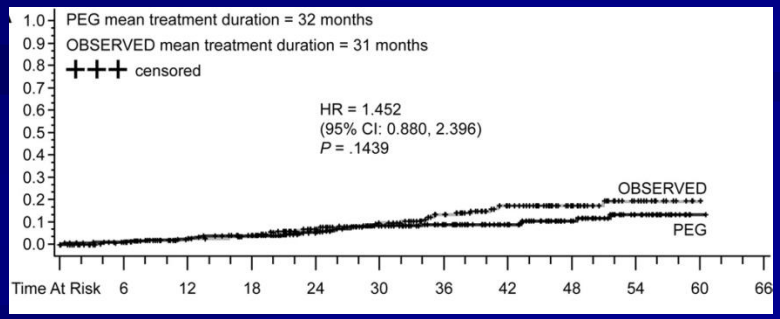
Evaluation of PegIntron in Control of Hepatitis C Cirrhosis (EPIC)

Patients HCV non répondeurs IFN + ribavirine (n = 311) vs no treatment n = 315)

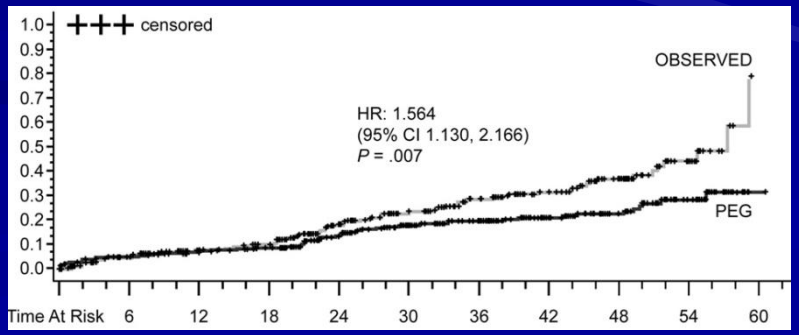
Incidence évènements : décompensation, CHC, décès ou TOH

	Contrôles	PegRiba	p
1er évènement clinique (%)	11	9	NS
Incidence CHC (%)	4	4	NS
Aggravation (%)	28	20	0,07
Décès (%)	2	2	NS

Temps 1er évènement clinique



Maladie évolutive



Vitamine K et CHC (1)

Kojimaet al., Hepatogastroenterology 2010

- Cirrhose virale C
- menatetrenone (n = 22, 4 5mg/j, po) vs contrôle (n = 18)
- **Incidence CHC : 9.1% vs 27.8%, NS**

Wei et al., Int J Cancer 2010

- Sorafenib et vitamine K induisent une apoptose dans CHC
- **Association vit K + sorafenib induit une inhibiton de la croissance et une apoptose des cellules de CHC**
- Inhibition de la voie RAF/mitogen-activated protein kinase/ERK

Chu KJ Asian J Surg. 2010

- méta-analyse (4 études)
- **Amélioration survie sans récidive après traitement curatif**
- Pas d'effet probant sur survie

Vitamine K et CHC (2)

Zhang et al., Oncol Rep. 2011

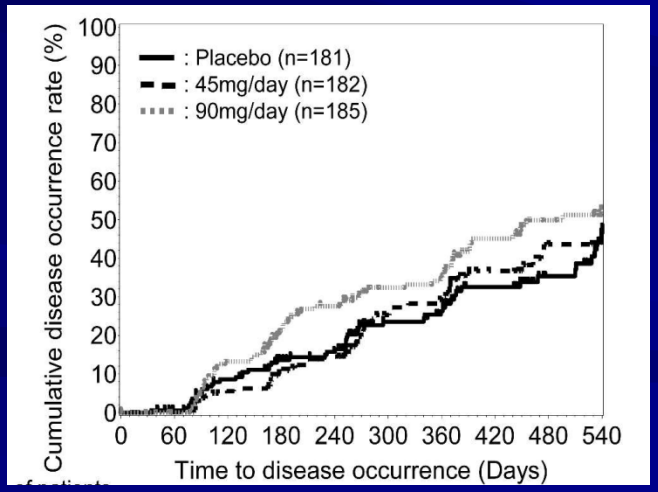
Vitamin K2 augments 5-fluorouracil-induced growth inhibition of human hepatocellular carcinoma cells by inhibiting NF-κB activation

Yoshida et al., Hepatology 2011

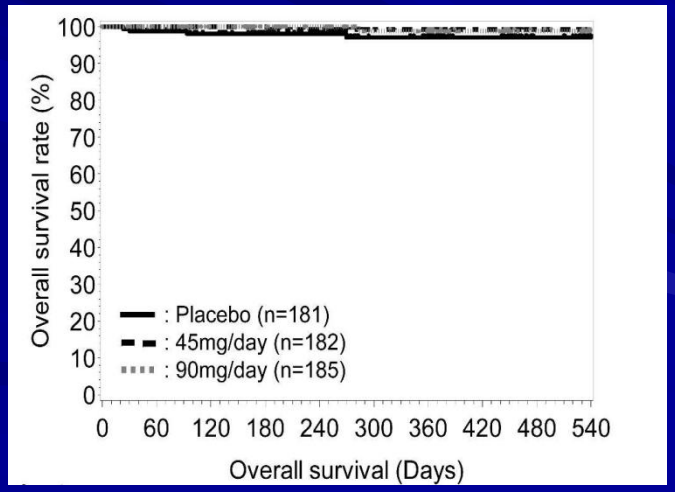
Prévention secondaire après traitement curatif

Randomisation placebo (n=181), 45 mg/j (n=182), 90 mg/j (n=185)

Survie sans récidive : HR = 1.150, (0.843 - 1.570), p=0,8



Incidence récidive



Survie globale

Resveratrol

- **Yu et al., Hepatogastroenterology. 2010**
  - **Resveratrol, polyphenol, baies, raisin et le vin**
  - **Inhibition de l'expression de VEGF sur cellules CHC (médié par NF-kappa)**
  - **Inhibition angiogénèse tumorale**

- **Bishayee Cancer Prev Res. 2010**
  - **Resveratrol alimentaire (50-300 mg/kg)**
  - **Supression du stress oxydatif et de la réponse inflammatoire dans l'hépatocarcinogénèse induite par du diethylnitrosamine**

Curcumin

Darvesh et al Curr Pharm Biotechnol. 2011

Rôle du stress oxidant et de l'inflammation dans l'hépatocarcinogénèse

Curcumin : source de polyphenols alimentaires = antioxidant

Revues des effets du curcumin in vitro et in vivo dans des modèles de CHC

- Effet antioxidant
- Apoptotique
- Anti-inflammatoire

Saffron: A potential target for a novel anti-cancer drug against hepatocellular carcinoma. Amin A et al.,. Hepatology 2011

Modele CHC-DEN, rat

Administration of saffron 75 mg/kg/j, 150 mg/kg/j et 300 mg/kg/j

2 semaines avant début injection DEN (rats) pdt 22 semaines

Réduction de incidence nodules hepatiques dyschromatiques.

Réduction fréquence et aire de foyers glutathione-S-transferase positifs.

Effet anti-oxidant

Effet anti-proliferative : diminution Ki-67, cyclooxygenase 2, iNOs, nfKb TNFr

Augmente apoptose

Café et CHC

Leung WW et al J Epidemiol Community Health. 2011

- Porteurs HBV chroniques (n =234)
- Etude cas-contrôles : 109 cases et 125 contrôles
- Consommation modérée de café
  - **Réduction risque de CHC : OR 0.54 (95% CI 0.30 to 0.97)**
  - **Effet dose-response (p=0,02)**
  - **Diminution du risque de CHC chez les buveurs alcoliques modérés : OR 0.41 (0.19 to 0.89)**

Masterton GS et al., Eur J Gastroenterol Hepatol. 2010

- "Coffee and the liver : a potential treatment for liver disease?"
- "An interventional study of coffee in patients with liver disease, is urgently required particularly because of the potential to reduce fibrosis and hepatocellular carcinoma risk"

Kalthoff et al, Gastroenterology 2010

- Induction de l'expression des **glucuronosyltransferases** par Nrf2 dans le foie et l'estomac
- Cultures cellules avec metal- or paper-filtre, décaffeiné ou instantané; thé vert ou noir, chocolat, ou produits métabolites de la cafeine
- Café induit la transcription de UGT1A1 et la glucuronisation pourrait induire les **effets protecteurs et anti oxydants** du café

Coffee consumption and reduced risk of hepatocellular carcinoma: findings from the singapore chinese health study.
Johnson S et al. Cancer Causes Control. 2011

Cohorte prospective : n= 63,257, 50 ans et plus.

Inclusions 1993 -1998

Décembre 2006: 362 CHC

Grande quantité de café ou caféine associé à une diminution du risque de CHC ($p < 0,05$)

≥ 3 tasses de café / j : 44% reduction du risque de HCC (hazard ratio 0.56, 95% confidence interval, 0.31-1.00, p = .049)

Pre-operative liver biopsy in cirrhotic patients with early hepatocellular carcinoma represents a safe and accurate diagnostic tool for tumour grading assessment.
Colecchia a et a J Hepatol. 2011

Pre-operative tumour grade can influence recurrence and survival after surgery

to determine the long-term safety and the overall accuracy

of PBH in assessing tumour grading in subjects who had undergone liver resection

Eighty-one cirrhotic patients with HCC

Tumour grading was scored according to a modified Edmondson-Steiner classification

Tumour grade was correctly identified by NCB in 74 out of 81 (91.4%) HCCs. NCB overall sensitivity and specificity were 65% and 98.1%, respectively, with a PPV of 92% and an NPV of 91%.

overall survival rates at 1, 3, and 5 years were 83%, 62%, and 44%, respectively; the recurrence rate after a 5-year-follow-up was 56.2% for low grade and 82.3% for high grade tumours ($p<0.007$)

Combining clinical, pathology, and gene expression data to predict recurrence of hepatocellular carcinoma
Villanueva GY 2011

70% of patients with hepatocellular carcinoma

Barcelona-Clinic Liver Cancer 0/A), single-nodule HCC

287 HCC patients undergoing resection

tumor (n = 287) and adjacent nontumor, cirrhotic tissue

Gene expression signatures that were associated with aggressive HCC were clustered

tumor-associated signature G3-proliferation (hazard ratio [HR], 1.75; P = .003)

and an adjacent poor-survival signature (HR, 1.74; P = .004) were independent

predictors of HCC recurrence, along with satellites (HR, 1.66; P = .04).

Radiofrequence vs resection

Huang J et al, Ann Surg. 2010: 230 HCC

RFA 1-, 2-, 3-, 4- and 5-year overall survival were 86.96%, 76.52%, 69.57%, 66.09%, 54.78%

RES 98.26%, 96.52%, 92.17%, 82.60%, 75.65%, (P = 0.001)

Recurrence-free survival rates for the 2 groups were 81.74%, 59.13%, 46.08%, 33.91%, 28.69% and 85.22%, 73.92%, 60.87%, 54.78%, 51.30%, respectively (P = 0.017)

The 1-, 2-, 3-, 4-, and 5-year overall recurrence rates were 16.52%, 38.26%, 49.57%, 59.13%, and 63.48% for the RFA group and 12.17%, 22.60%, 33.91%, 39.13%, and 41.74% for the RES group. (P = 0.024)

Huang J et al : J Gastrointest Surg. 2011

Childs A cirrhotics = 1,061 cases: a retrospective study.

The 5-year OS and corresponding RFS as well as DFS were significantly higher in the surgical resection group compared with the RFA group ($p < 0.001$, $p < 0.001$, $p < 0.001$

Childs A cirrhotic patients with solitary HCC larger than 3 cm but less than 5 cm, or with two or three lesions each less than 5 cm, surgical resection provides a better survival than RFA

Repeated radiofrequency ablation for management of patients with cirrhosis with small hepatocellular carcinomas: a long-term cohort study.
Rossi s et al, Hepatology. 2011

Retrospective analyze of a prospective series of 706 patients with cirrhosis (Child-Pugh class ≤ B7)

RFA for 859 HCC ≤ 35 mm in diameter (1-2 per patient)

465 (66.8%) of the 696 patients with CRs experienced a first

recurrence at an incidence rate of 41 per 100 person-years (local recurrence 6.2; nonlocal 35)

Overall, there were 877 episodes of recurrence (1-8

per patient); 577 (65.8%) of these underwent RFA that achieved CRs in 557 (96.5%)

cases. No procedure-related deaths occurred in 1,921 RFA sessions. Estimated 3-

and 5-year overall and disease-free (after repeated RFAs) survival

Midterm Outcomes in Patients With Intermediate-Sized Hepatocellular Carcinoma

A Randomized Controlled Trial for Determining the Efficacy of Radiofrequency Ablation Combined With Transcatheter Arterial Chemoembolization

Cancer December 1, 2010

n= 37,solitary HCCs intermédiate (31-50 mm)

TACE-RFA group, on the same day, vs RFA

3 years rates of local tumor progression RFA 39% and TACE-RFA groups 6%, P=0,012.

3-year survival rates : RFA 80% vs TACE-RFA 93%, NS

.

Combined transarterial chemoembolization and 3-dimensional conformal radiotherapy for hepatocellular carcinoma with main portal vein thrombosis.
Park et al., Hepatogastroenterology. 2010

18 patients, unresectable HCC with MPVT and underwent combined TAE and 3D-CRT

The overall survival for the 18 patients was 13.0 +/- 8.5 months

For the MPVT, an objective response was observed in 10 out of the 18 cases.

AFP level, presence of regional lymph node metastasis, main tumor response and the MPVT response were prognostic factors for survival

as 3 days after bevacizumab administration in patients with

HCC. These early changes in tumor perfusion may be predictive of tumor response

at 2 months, progression-free survival, and overall survival, and they may be

potential surrogate measures of the effectiveness of antiangiogenic therapy in

Transarterial (chemo)embolisation for unresectable hepatocellular carcinoma.

Cochrane Database Syst Rev. 2011 Mar 16;3

- all randomised trials that compared TACE or TAE versus placebo
- 9 trials with 645 participants 6 TACE, 3 TAE
- TACE or TAE versus control does not significantly increase survival (HR 0.88; 95% CI 0.71 to 1.10)
- no firm evidence to support or refute TACE or TAE for patients with unresectable HCC

Thérapies ciblées

- Gastroenterology Villanueva llovet
- no specific oncogene addictions are yet known to be implicated in HCC progression, so it is important to improve our understanding of its

  molecular pathogenesis

- tyrosine kinase inhibitor (TKI) 1ére ligne : sorafenib, erlotinib, linifanib)
- 2éme igne : brivanib, everolimus, monoclonal antibodies (eg, ramucirumab) are being tested as second-line therapies
- Identification of oncogenes that mediate tumor progression, and trials that monitor their products as biomarkers, might lead to personalized therapy

- **GY 2011 140 page 1410 et page 1501**

Evaluation réponse au sorafénib

Shao et al Cancer. 2010

N = 72 : 12 of those patients (17%) early AFP responders (decline >20% from baseline after 2 to 4 weeks)

- improved overall response rate (33% vs 8%; P=.037)
- improved disease control rate (83% vs 35%; P=.002), (objective response plus stable disease for a minimum of 8 weeks)
- increase in median progression-free survival 7.5 vs 1.9 months; P=.001
- increase in median overall survival : 15.3 vs 4.1 months; P=.019

Doxorubicin plus sorafenib vs doxorubicin alone in patients with advanced hepatocellular carcinoma: a randomized trial.
abou-alfa gk, jama. 2010

Doxorubicin plus sorafenib vs doxorubicin alone in patients with advanced HCC and Child-Pugh A disease.

double-blind phase 2 multinational study, from Apr 2005 - Oct 2006, 96 patients (76% male; median age, 65 years [range, 38-82 years])

60 mg/m(2) of doxorubicin intravenously every 21 days plus either 400 mg of sorafenib or placebo orally twice a day

median time to progression was 6.4 months in the sorafenib-doxorubicin group (95% confidence interval [CI], 4.8-9.2), and 2.8 months (95% CI, 1.6-5) in the doxorubicin-placebo monotherapy group (P = .02)

Median overall survival was 13.7 months (95% CI, 8.9--not reached) and 6.5 months (95% CI, 4.5-9.9; P = .006), and progression-free survival was 6.0 months (95% CI, 4.6-8.6) and 2.7 months (95% CI, 1.4-2.8) in these groups, respectively (P = 0.006).

Dynamic contrast-enhanced magnetic resonance imaging biomarkers predict survival and response in hepatocellular carcinoma patients treated with sorafenib and metronomic tegafur/uracil.

Hsu CY J Hepatol. 2011.

- correlation of vascular response measured by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and the clinical outcome
- Sorafenib (800 mg/day) plus tegafur/uracil (250 mg/m(2) /day based on tegafur)
- dynamic contrast-enhanced magnetic resonance imaging (DEC MRI) at baseline and after 14 days of treatment
- N = 31
- After 14 days of study treatment, the median K(trans) change was -47.1% (range -87.0 - -18.0%) in patients with PR or SD, and 9.6% (range -44.8 - +81%) in those with PD ($p < 0.001$)
- A vascular response, defined by a 40% or greater decrease in K(trans) after 14 days of study treatment, correlated with longer progression-free survival (median 29.1 vs. 8.7 weeks, $p = 0.033$) and overall survival (median 53.0 vs. 14.9 weeks, $p = 0.016$).

Phase II, open-label study of brivanib as first-line therapy in patients with advanced hepatocellular carcinoma. Park et al Clin Cancer Res. 2011.

- phase II open-label study of brivanib as first-line therapy in patients with unresectable or metastatic
- Brivanib : orally at a dose of 800 mg once daily
- 55 patients
- 6 month progression-free survival
- rate : 18.2% (9.1%-30.9%).
- Median progression-free survival : 2.7 months (1.4-3.0).
- One patient achieved a complete response and three
- achieved a partial response. Twenty-two had stable disease.
- Median overall survival 10 (6.8-15.2) months.

Role of the easl, recist, and who response guidelines alone or in combination for hepatocellular carcinoma: radiologic-pathologic correlation.
Riaz et al; J Hepatol. 2011

Comparaisos courbes ROC

Median times (95% CI) to the WHO, RECIST, and EASL responses were 5.3 (4-11.5), 5.6 (4-11.5), and 1.3months (1.2-1.5)

The product of WHO and EASL demonstrated better ROC than the individual guidelines for assessment of tumor response.
EASL×WHO scoring system

provides a simple and clinically applicable method of response assessment

following locoregional therapies for hepatocellular carcinoma.

Clearance of Hepatitis B Surface Antigen and Risk of Hepatocellular Carcinoma in a Cohort Chronically Infected with Hepatitis B Virus

Simonetti et al (HEPATOLOGY 2010;51:1531-1537.)

cohort study 1,271 (Alaska)

Chronic HBV infection , follow up = 19.6 years

HBsAg clearance of 0.7%/year

6patients developed HCC a mean of 7.3 years after HBsAg clearance (range, 2.0-15.5 years).

The incidence of HCC after clearance of HBsAg 36.8 per 100,000 per year (95% CI 13.5-80.0)

significantly lower than the rate in HBsAg-positive (195.7 cases per 100,000 person-years of follow-up [95% CI 141.1-264.5; $P < 0.001$]).

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Wanf et al., Liver Int. 2010

10 RCTs, n = 595, TACE + PA (RFA, PEI) vs monotherapy

improvement overall survival 1year-OR=2.28 (1.14-4.57; P=0.020], 2 year-OR=4.53, (2.62-7.82 ; P<0.00001) and 3-year-OR=3.50 (1.75-7.02, P=0.0004)

Meta-analysis of radiofrequency ablation versus hepatic resection for small hepatocellular carcinoma

Zhou *et al. BMC Gastroenterology* 2010, **10**:78

	Résection	Radiofréquence	p
Survie globale (%)			
3 ans	74,4	63,5	<0,001
5 ans	51,9	41,3	0,05
Récidive (%)	4,2	19	< 0,001
Survie sans récidive (%)			
1 an	80,3	68,8	0,006
3 ans	54,4	34,9	<0,001
5ans	23,8	18,4	0,05
Morbidité	32,5	9,6	0,003
Mortalité (%)	0,8	0,1	NS

The combination of sorafenib with transarterial chemoembolisation for hepatocellular carcinoma

R. Cabrera*, D. S. Pannu†, J. Caridi‡, R. J. Firpi*, C. Soldevila-Pico*, G. Morelli*, V. Clark*, A. Suman*, T. J. George Jr.§ & D. R. Nelson*

Aliment Pharmacol Ther 2011

n = 47, HCV (60%), cirrhosis CP : A 72%; B 28%
(BCLC : B 81%, BCLC C 19%, median AFP 24ng/mL
Suivi médian 12 mois, temps médian de Sorafenib 6 mois

Table 5 | Tumour response at 6 months

Amended RECIST at 6 months	*N* (%)
Complete response	11 (26.8)
Partial response	12 (29.3)
Stable disease	5 (12.2)
Progression of disease	13 (31.7)
Disease control rate*	28 (68.2)
Objective response rate†	23 (56.1)

Survie globale (médiane) :
18,5 mois (16,1-20,9)

Toxicité plus intense post CEL ?