

SIEMC

Società Italiana di Ecografia  
in Medicina e Chirurgia

II CORSO NAZIONALE E  
SEMINARI DI  
ECOGRAFIA CLINICA  
SIEMC



RIMINI,  
4 - 7 OTTOBRE 2015  
AQUA HOTEL + ARIA HOTEL

**Fabio Fornari**

**Impatto clinico della diagnosi di HCC**

# Le peculiarità del Carcinoma Epatocellulare

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1. Il tumore si sviluppa nel contesto di fattori di rischio ambientali ben conosciuti.
  2. Il tumore è strettamente associato con una malattia cronica di fegato, principalmente con la cirrosi.
  3. Il solo tumore maligno che non necessita per la diagnosi della conferma istologica.
  4. Il solo tumore maligno solido trattabile con il trapianto dell'organo.
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# Impatto clinico della diagnosi di HCC

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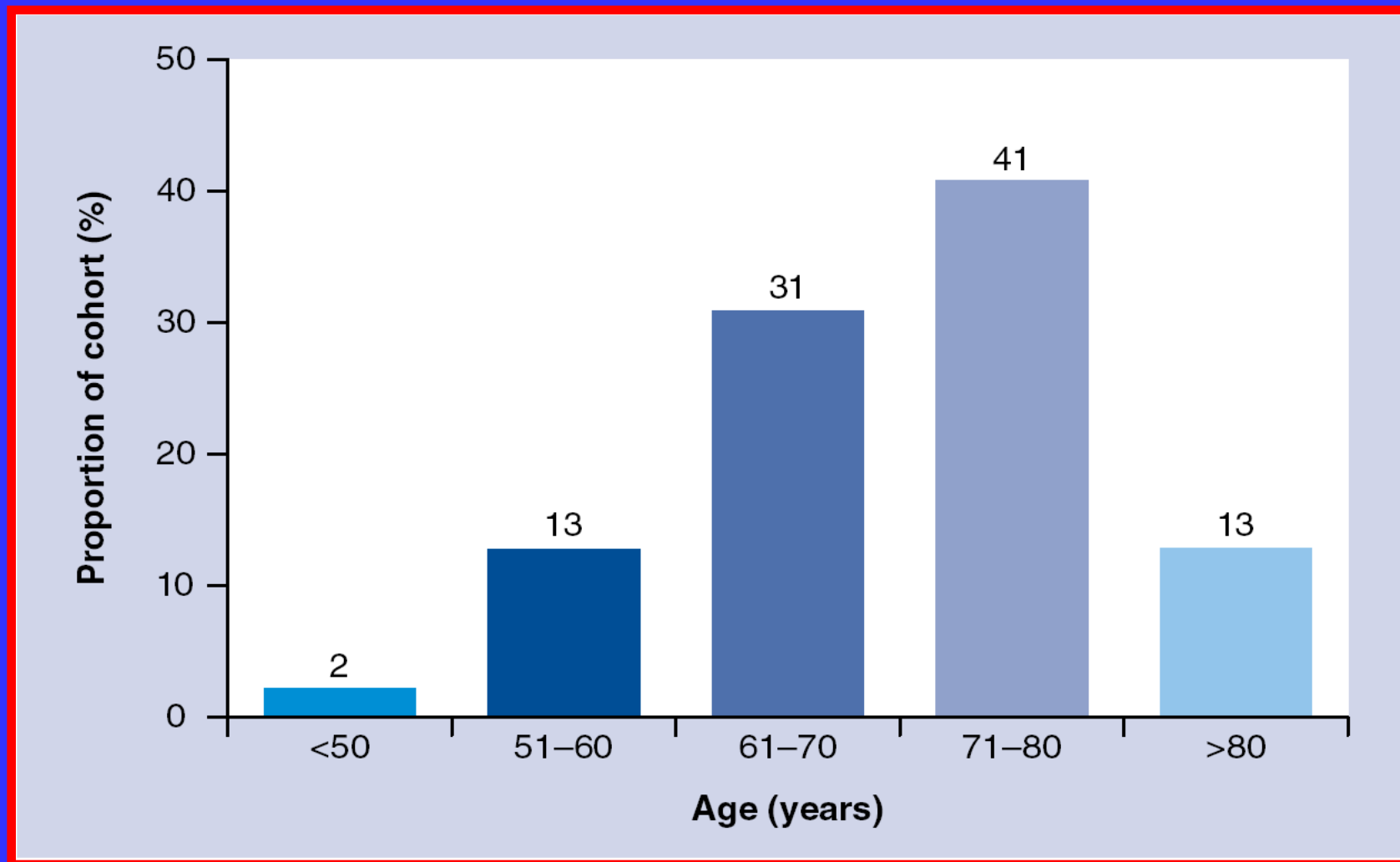
I dati epidemiologici più recenti  
ed i nuovi fattori di rischio

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## Position paper of the AISF : the multidisciplinary clinical approach to hepatocellular carcinoma (Dig. Liver Dis . 2013 )

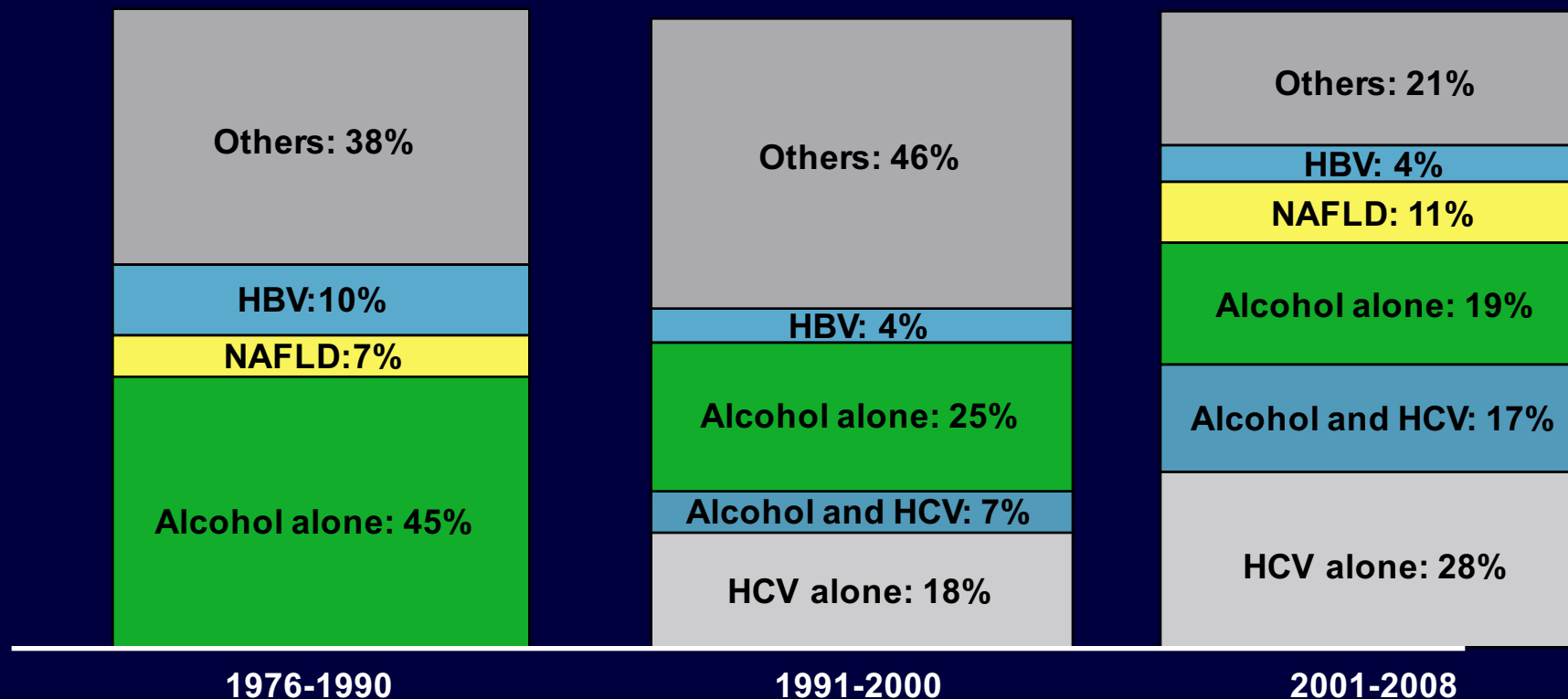
- In Italia l'HCC rappresenta il settimo più frequente tumore nei maschi e il tredicesimo più comune nelle femmine , con una prevalenza di 53/100.000 negli uomini e 22/100.000 nelle donne.
- Rappresenta la quinta causa di mortalità nei maschi e la settima nelle femmine .
- Nel 2009 i tassi di mortalità appaiono in diminuzione rispetto al 2000 . La sopravvivenza a 5 anni è pari al 15% .
- Nella maggior parte dei casi, l'HCC insorge su fegato cirrotico ; HCV (49%) , alcool (21%) , eziologie miste (12%) e HBV (13%) le cause più frequenti.

**Classi di età nella coorte di 536 pazienti italiani (età media 70 anni )**  
Alcool (23%) ; HBV (11,5%) ; HCV (54,1%) ( maschi 71%)

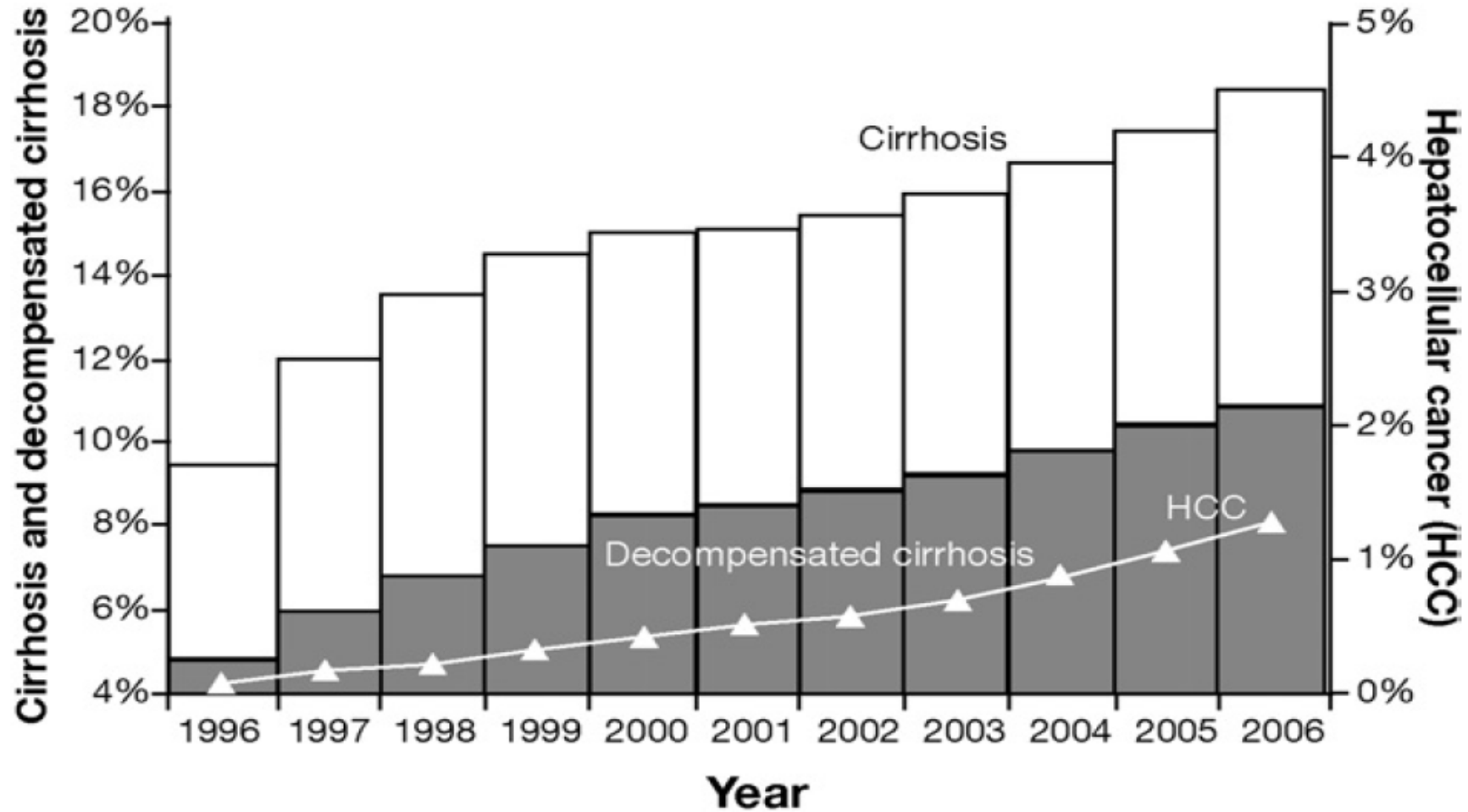


# Trends in HCC Etiology

- ~50% increase in HCV-related HCC between 1991-2008

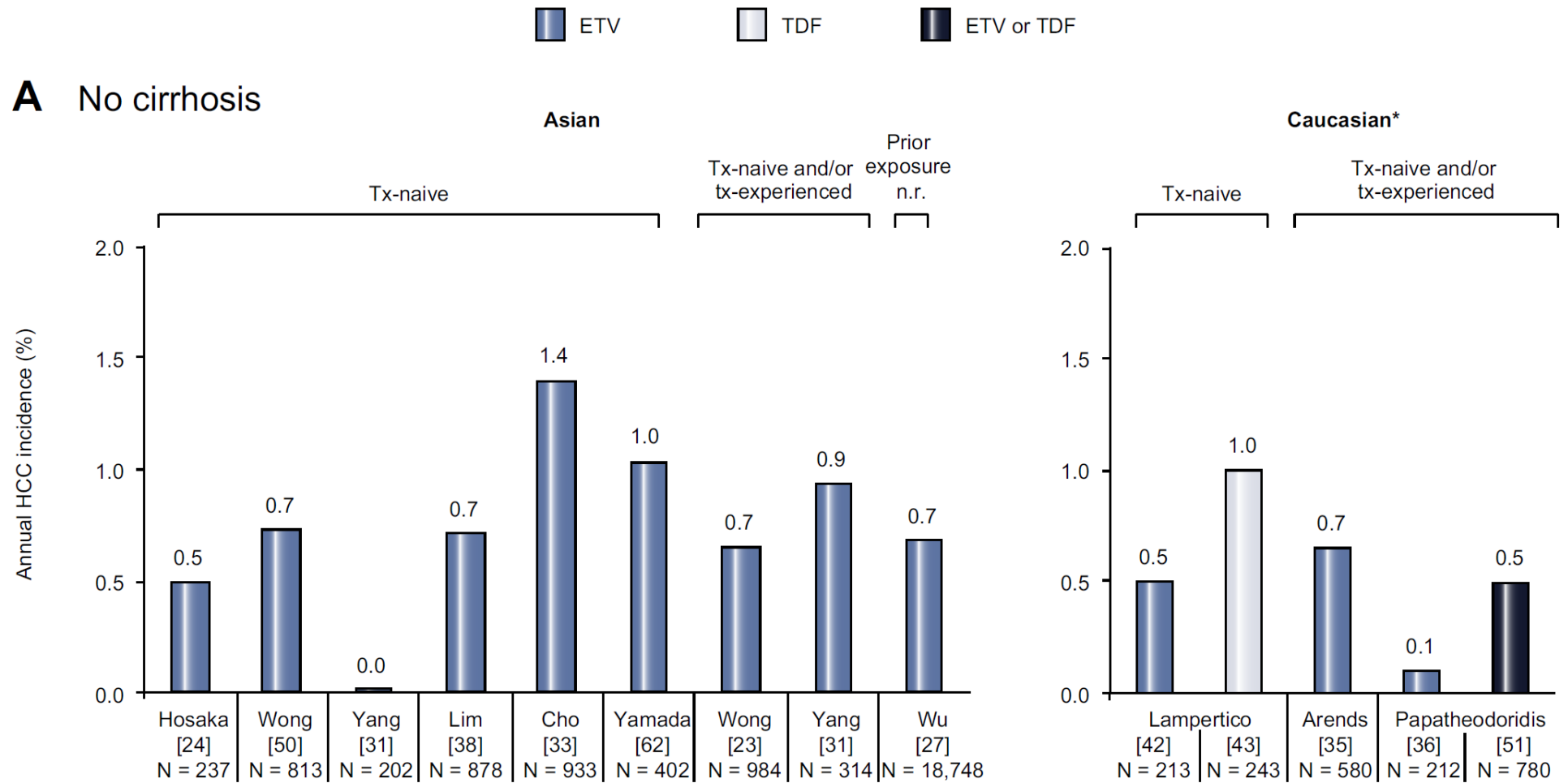


Aumentata prevalenza di HCC e cirrosi in una coorte di 106,242 pazienti con infezione cronica da HCV



Kanwal et al Gastroenterology April 2011

# Incidenza annuale di HCC in pazienti con epatite cronica HBV-correlata senza cirrosi in terapia con ETV o TDF

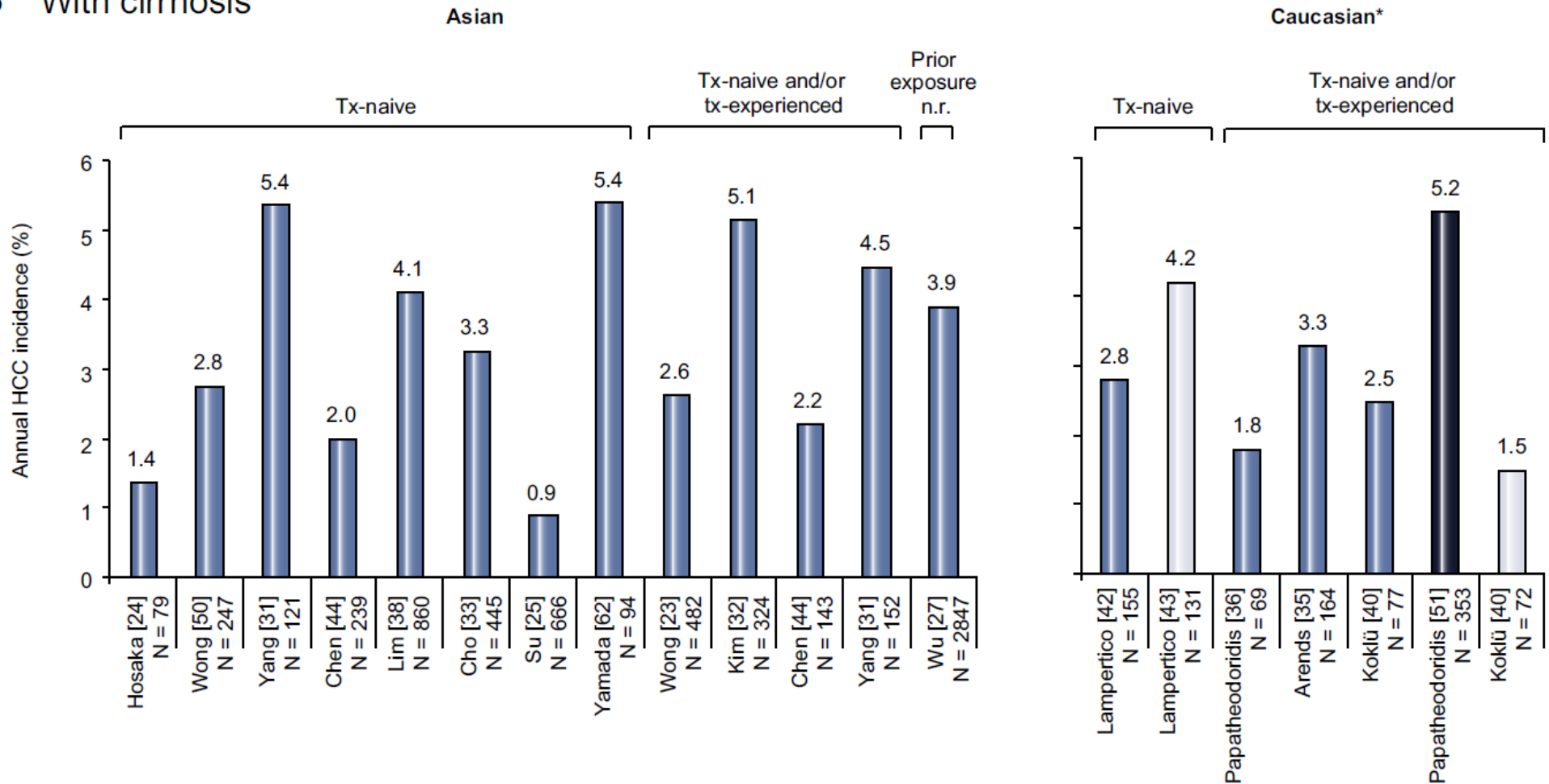


Papatheodoridis et al J Hepatology 2015

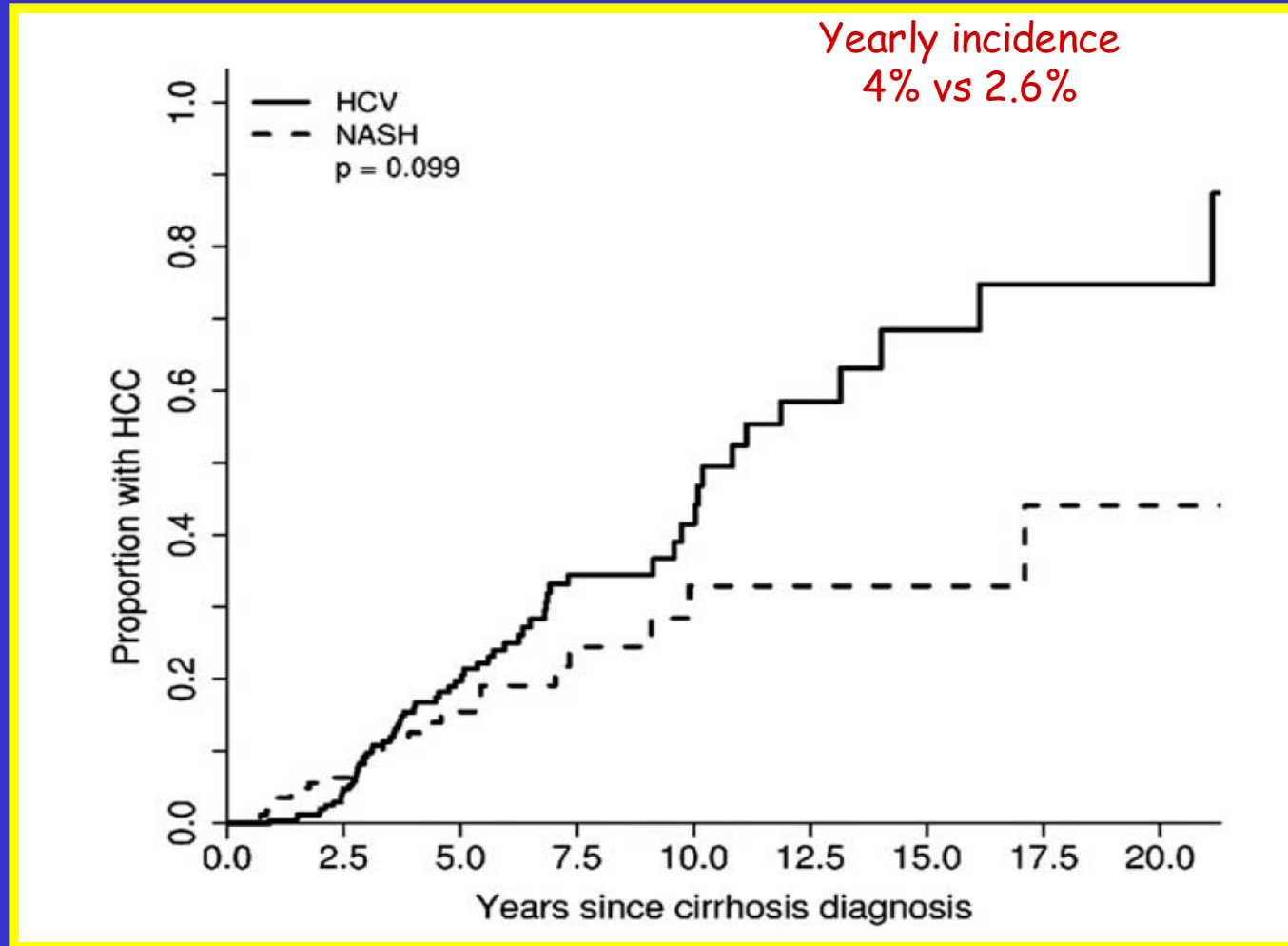


# Incidenza annuale di HCC in pazienti con epatopatia cronica HBV- correlata con cirrosi

## B With cirrhosis



# Annual cumulative incidence of HCC in 315 HCV and 195 NASH cirrhotic patients



Ascha et al Hepatology 2010

## Hepatocellular cancer: The impact of obesity, type 2 diabetes and a multidisciplinary team

Jessica Dyson<sup>1,†</sup>, Bryan Jaques<sup>2,†</sup>, Dipankar Chattopadhyay<sup>2,3</sup>, Rajiv Lochan<sup>2</sup>, Janine Graham<sup>4</sup>, Debasish Das<sup>1</sup>, Tahira Aslam<sup>5</sup>, Imran Patanwala<sup>1</sup>, Sameer Gaggar<sup>1</sup>, Michael Cole<sup>3</sup>, Kate Sumpter<sup>2,4</sup>, Stephen Stewart<sup>1,6</sup>, John Rose<sup>5</sup>, Mark Hudson<sup>1</sup>, Derek Manas<sup>2</sup>, Helen L. Reeves<sup>1,2,3,\*</sup>

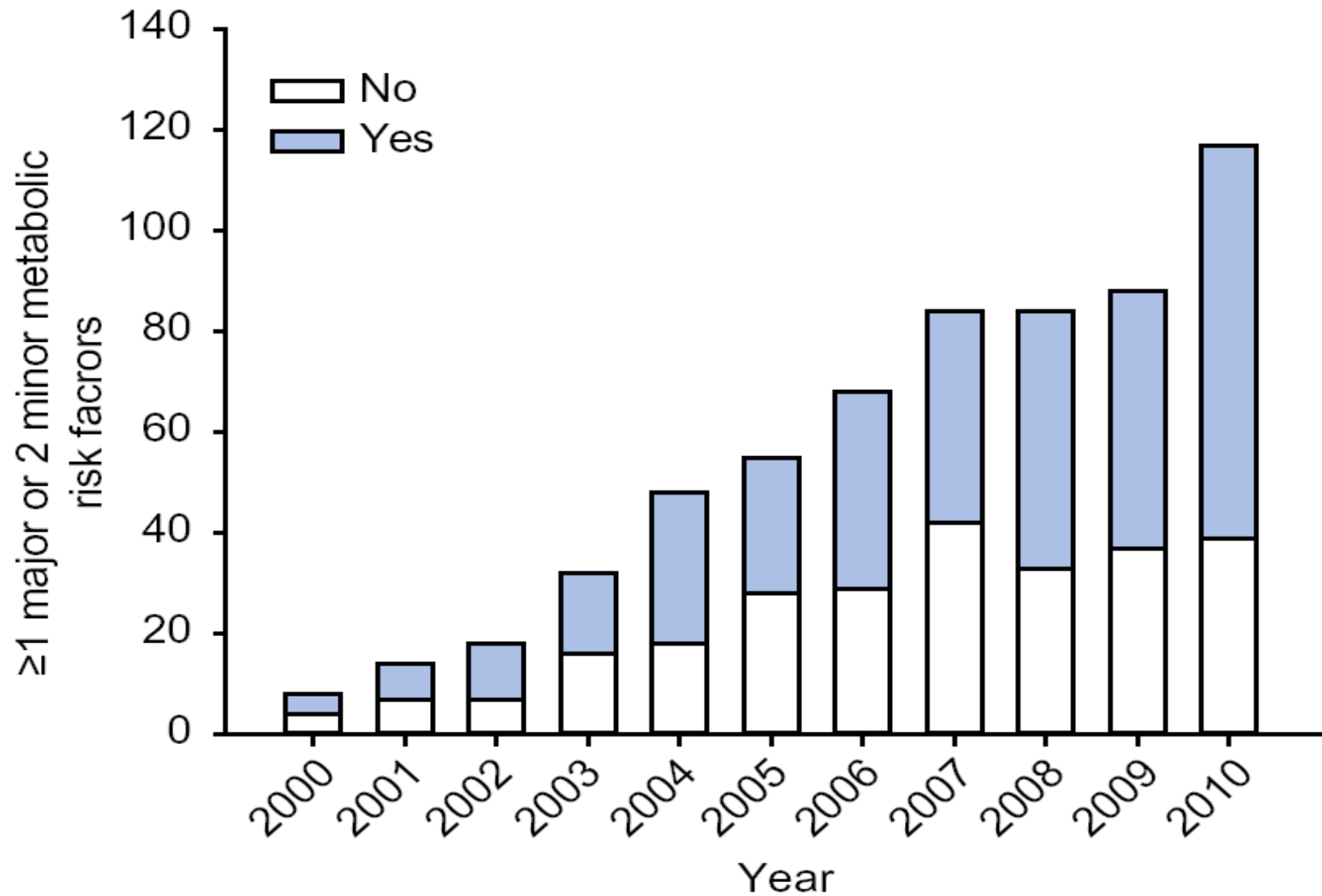
<sup>1</sup>The Liver Group, Department of Medicine, Freeman Hospital, Newcastle-upon-Tyne Hospitals NHS Foundation Trust, UK; <sup>2</sup>Hepatopancreatobiliary Team, Freeman Hospital, Newcastle-upon-Tyne Hospitals NHS Foundation Trust, UK; <sup>3</sup>Northern Institute for Cancer Research, Newcastle University, Newcastle-upon-Tyne, UK; <sup>4</sup>Northern Centre for Cancer Care, Freeman Hospital, Newcastle-upon-Tyne Hospitals NHS Foundation Trust, UK; <sup>5</sup>Department of Radiology, Freeman Hospital, Newcastle-upon-Tyne Hospitals NHS Foundation Trust, UK; <sup>6</sup>Centre for Liver Disease, Mater Misericordiae University Hospital, Dublin, Ireland

La mortalità per HCC dal 2000 al 2010 è aumentata di quasi il doppio ( da 2 a 3.7 /100.00 ), con un incremento di 10 volte per le diagnosi di HCC ( età media da 57 a 70 anni).

Tale incremento è stato di 2-3 volte per le epatopatie HCV e alcool-correlate e di oltre 10 volte per i pazienti con NAFLD .

I pazienti con HCC associato a NAFLD erano più anziani , meno frequentemente sottoposti a sorveglianza e con più bassa prevalenza di cirrosi ( 77,2% ).

# Prevalenza dei fattori di rischio metabolici in pazienti con HCC in nord UK



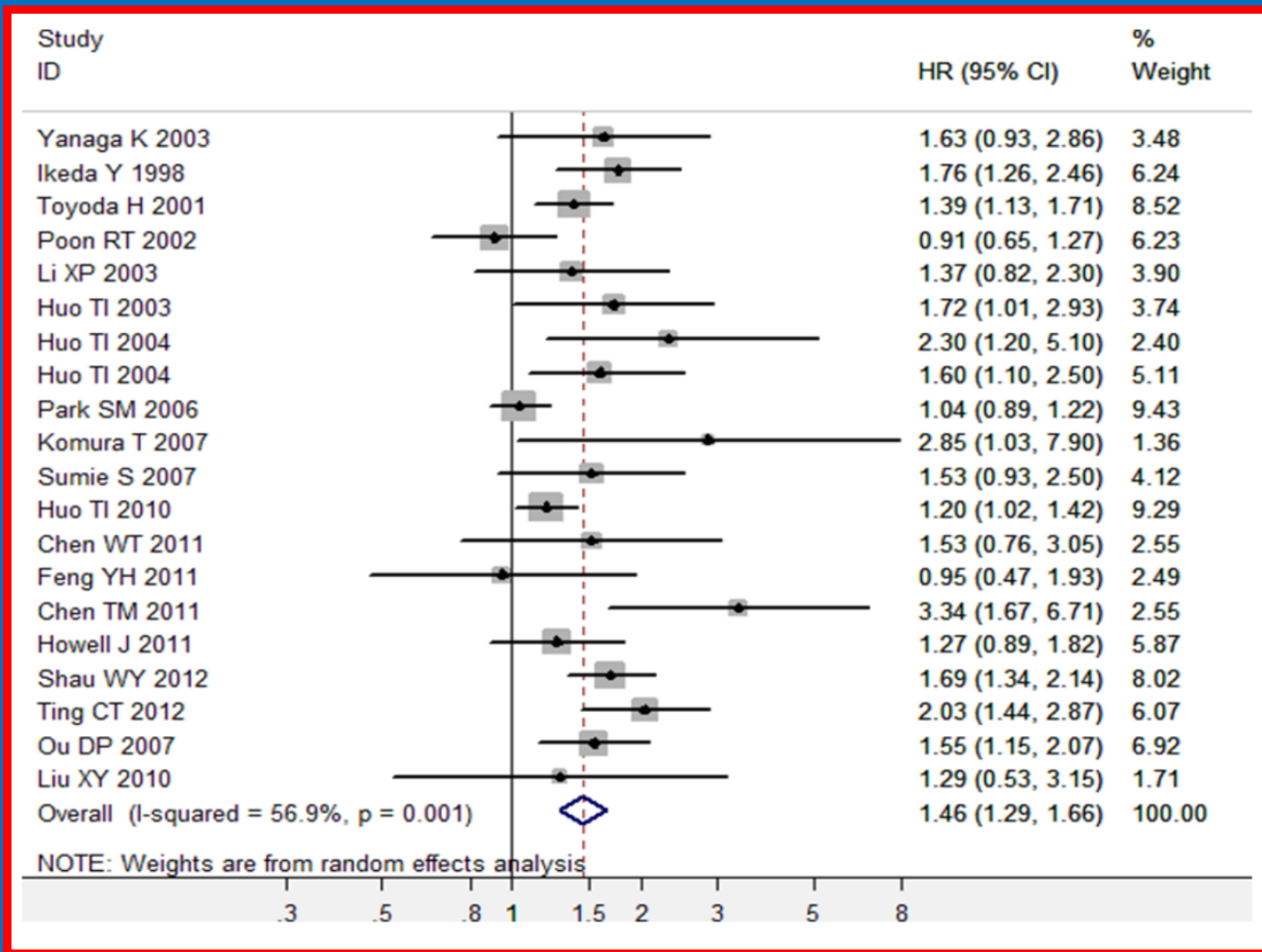
Dyson et al J Hepatology 2014

**NASH is the most rapidly growing indication for LT in patients with HCC in the U.S.** (Wong et al . Hepatology , June 2014)

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1. Inclusi nello studio 61.868 pazienti sottoposti a trapianto epatico dal 2002 al 2012 , **di cui 10.061 per HCC**
  2. **La eziologia principale** dell' epatopatia rimane **l'HCV** (49,9% nel 2012 vs 43,4% nel 2002) .
  3. **Un significativo incremento** è stato notato **negli HCC NASH-correlati** ( 6,5% nel 2012 vs 0% nel 2002)
  4. Un significativo **decremento** è stato osservato negli **HCC HBV-correlati** ( 4,6% nel 2012 vs 10,2% nel 2002)
-

# Meta-analisi di associazione fra diabete mellito e sopravvivenza globale per HCC





# L'obesità nel giovane adulto aumenta il rischio di HCC

(Hassan et al . Gastroenterology , July 2015)

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1. Inclusi nello studio 622 casi di HCC e 660 controlli sani
  2. L'obesità nel giovane adulto ( 20-40 anni) comporta un incremento del rischio di HCC pari al 2,6 volte con una insorgenza più precoce del tumore.
  3. Si osserva anche un'azione sinergica fra infezioni virali e obesità
  4. L'obesità non influenza la sopravvivenza globale dei pazienti con HCC
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# EASL Guidelines for Hepatocellular Carcinoma

Journal of Hepatology 35 (2001) 421–430

## Clinical Management of Hepatocellular Carcinoma. Conclusions of the Barcelona-2000 EASL Conference

Jordi Bruix\*, Morris Sherman, Josep M. Llovet, Michel Beaugrand, Riccardo Lencioni, Andrew K. Burroughs, Erik Christensen, Luigi Pagliaro, Massimo Colombo, Juan Rodés, for the EASL Panel of Experts on HCC

Clinical Practice Guidelines



## EASL–EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma

European Association for the Study of the Liver\*,  
European Organisation for Research and Treatment of Cancer

**Contributors:** **Chairmen:** Josep M. Llovet (EASL); Michel Ducreux (EORTC). **Clinical Practice Guidelines Members:** Riccardo Lencioni; Adrian M. Di Bisceglie; Peter R. Galle; Jean Francois Dufour; Tim F. Gieten; Eric Raymond; Tania Roskams; Thierry De Baere; Michel Ducreux; and Vincenzo Mazzaferro. **EASL Governing Board Representatives:** Mauro Bernardi. **Reviewers:** Jordi Bruix; Massimo Colombo; Andrew Zhu.

Journal of Hepatology 2012 vol. 56 | 908–943

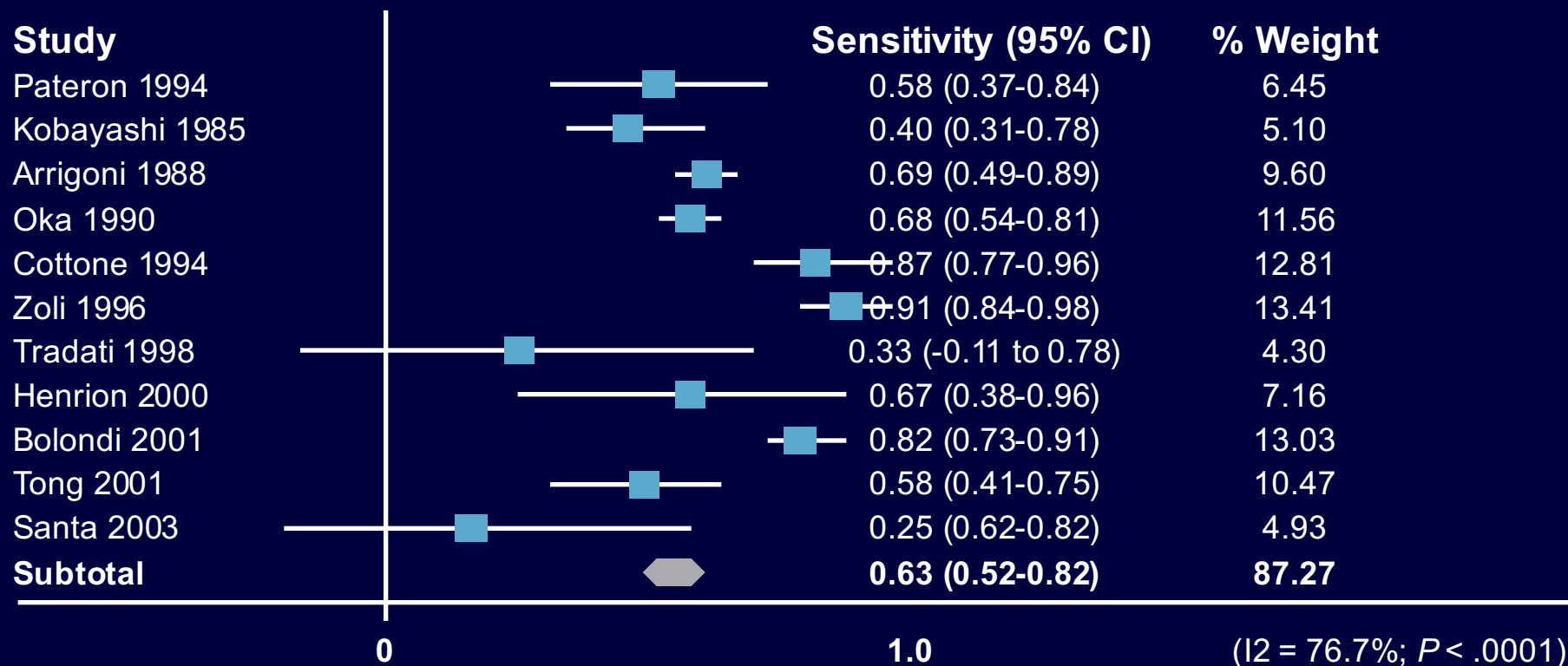
# Impatto clinico della diagnosi di HCC

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Le strategie di screening e  
sorveglianza

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# Ultrasound Surveillance in Early HCC: Systematic Review



- AFP improves detection to 70%
- Every 6 mos significantly better than 12 mos

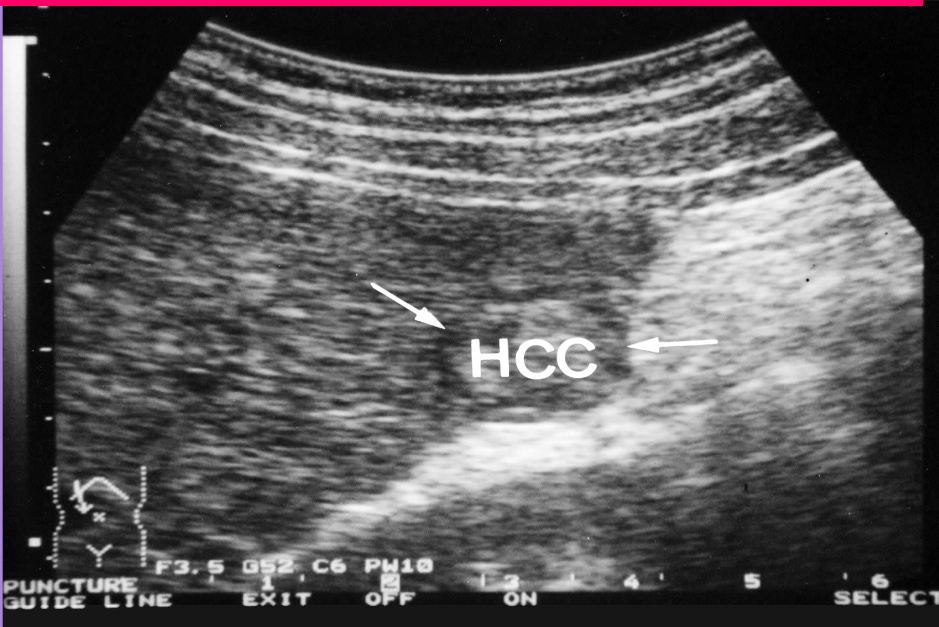
# ULTRASONOGRAPHIC PATTERNS OF SMALL HCC

OSP. PIA  
DIV. GAS



1: ADDOME

22-07-  
10:53:  
ID:  
FOCUS  
1004



F3.5 G52 C6 PH10  
PUNCTURE GUIDE LINE EXIT OFF ON SELECT

OSP. PIACENZA IDI  
DIV. GASTRO

Y] 02.09.03  
12:55:34  
1CV 3.5M  
PWR: 100%

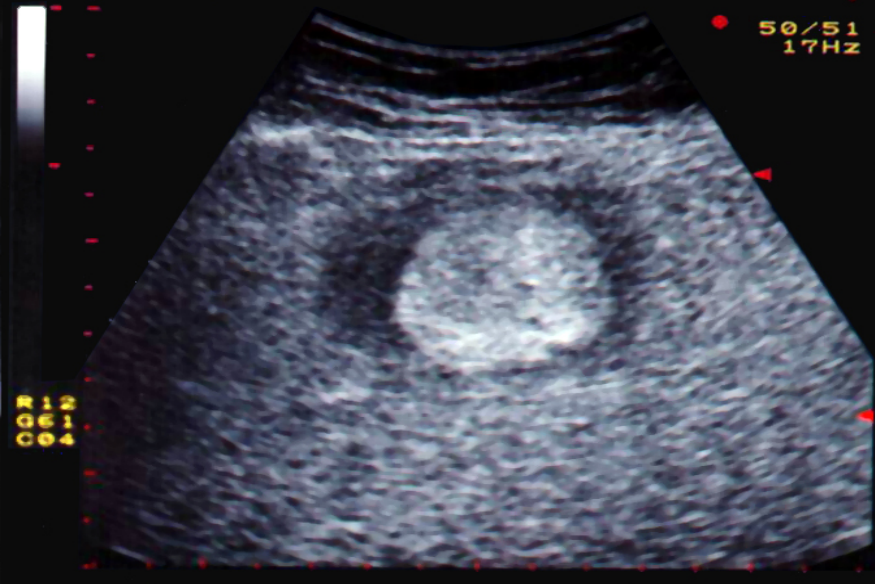
47/49  
17Hz



1: ADDOME

OSP. PIACENZA IDI  
DIV. GASTRO

Y] 03.16.03  
12:26:38  
1CV 3.5M  
50/51 PWR: 100%  
17Hz



1: ADDOME

R12  
G04  
C04

R12  
G04  
C04



# Il dosaggio di AFP è utile nella sorveglianza per HCC ( Chang et al , AJG , giugno 2015 )

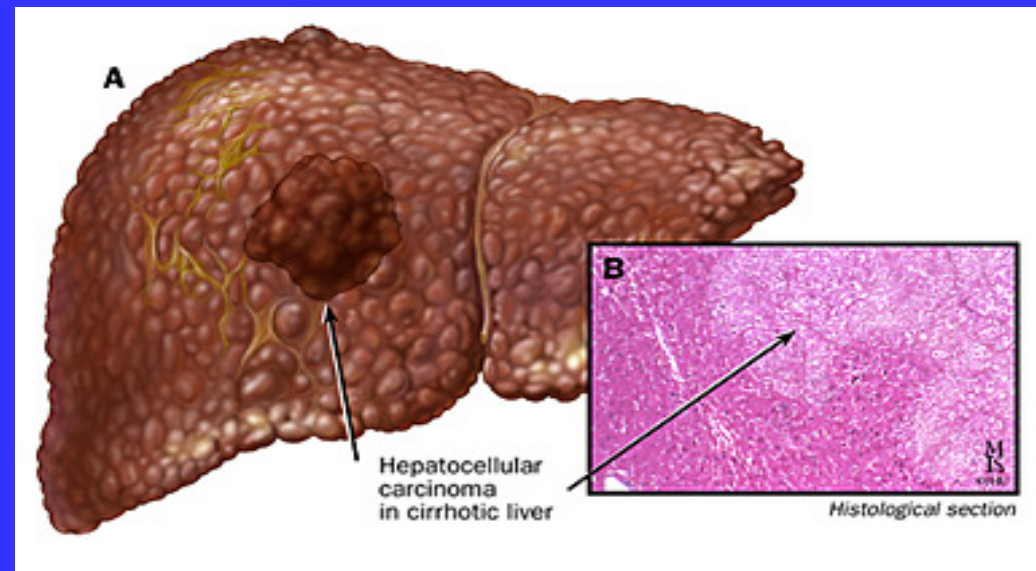
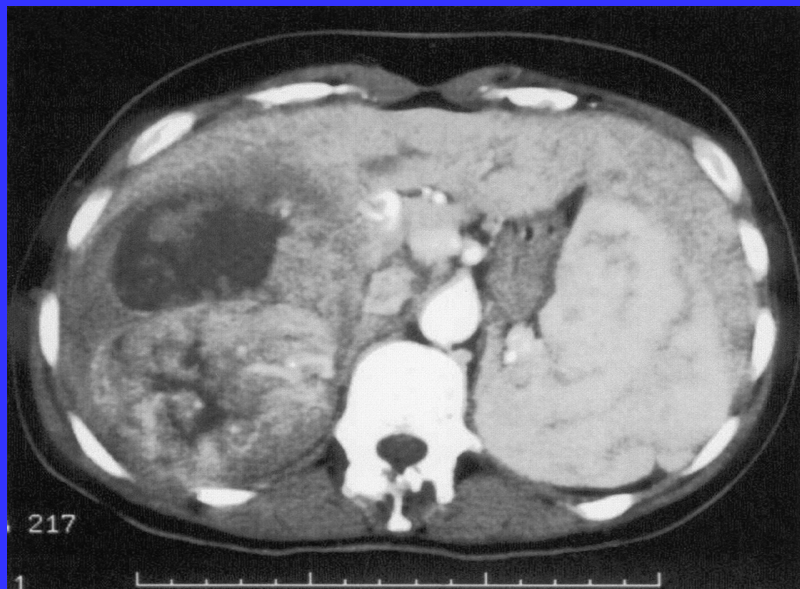
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1. Inclusi nello studio 1597 pazienti cirrotici con un follow-up mediano di 4,75 anni . Evoluzione in HCC nel 22,7% .
  2. Sensibilità e specificità di AFP 52,9 e 93,3% e di US del 92 e 74,2% .
  3. L'utilizzo combinato di AFP e US comporta sensibilità del 99,2 e specificità del 68,3%
  4. Utile valutare un incremento dei valori di AFP > 2 volte nell'ultimo anno
-



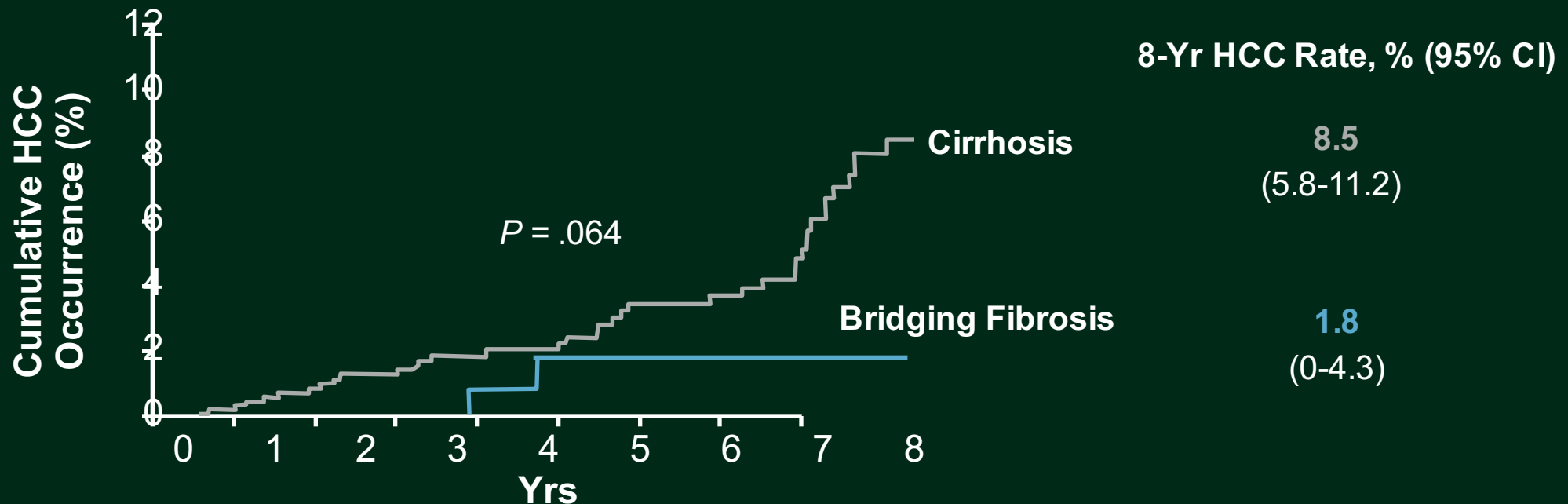
# Categories of patients in whom surveillance is recommended

1. Cirrhotic patients, Child-Pugh stage A and B\*
2. Cirrhotic patients, Child-Pugh stage C awaiting liver transplantation\*\*
3. Non-cirrhotic HBV carriers with active hepatitis or family history of HCC\*\*\*
4. Non-cirrhotic patients with chronic hepatitis C and advanced liver fibrosis F3\*\*\*\*



# Meta-analysis: Risk of HCC in HCV Pts With Advanced Fibrosis Following SVR

- 1000 patients with bridging fibrosis or cirrhosis who achieved SVR following IFN-based HCV therapy followed for median of 5.7 yrs
- Cirrhotics at greatest risk of HCC following SVR



# Incidenza di HCC dopo sieroconversione di HBsAg nei pazienti con epatite cronica HBV-correlata

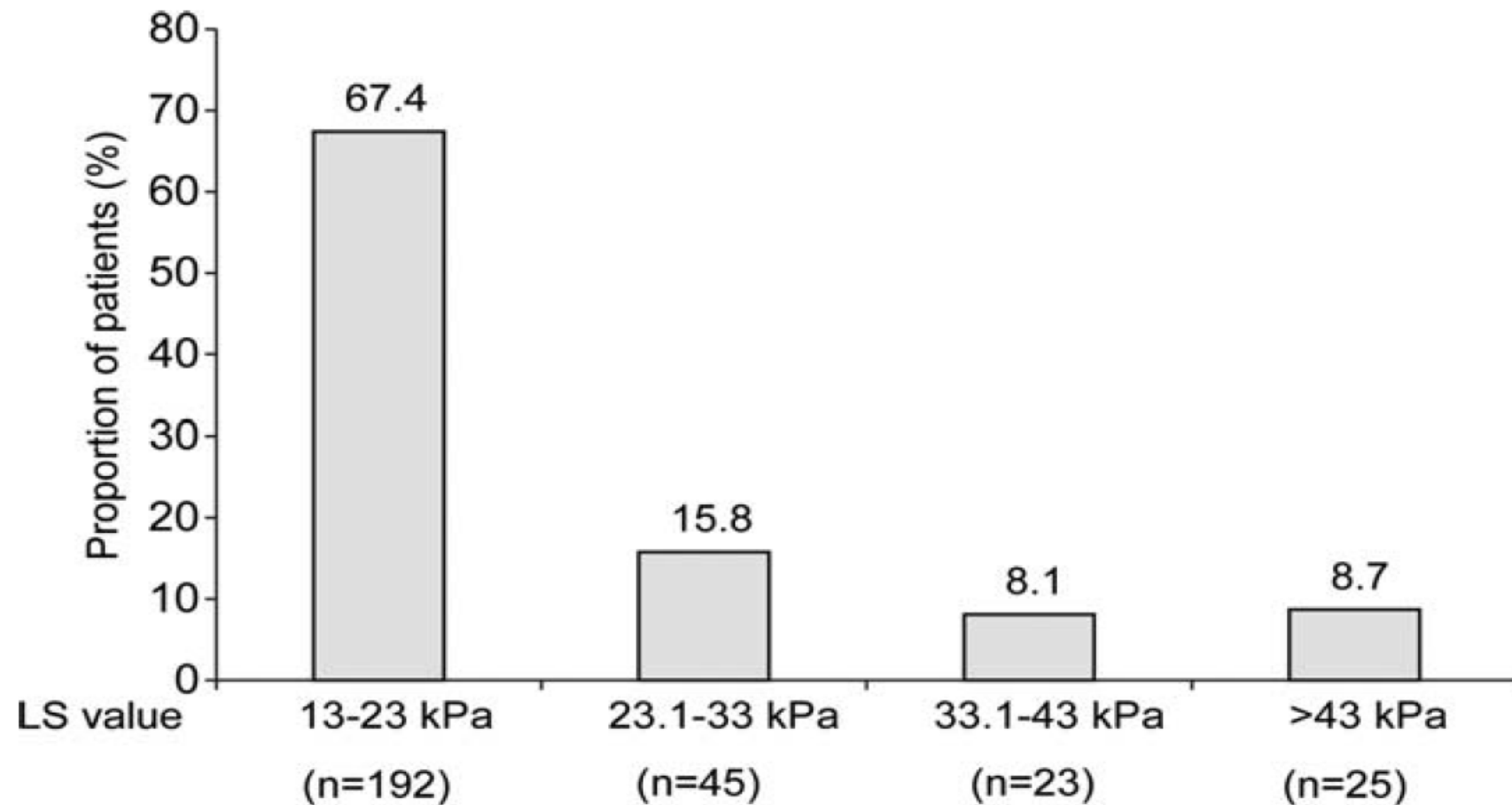
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1. Studio coreano retrospettivo di 829 pazienti HBV-infetti dopo perdita di HBsAg (età media 52 anni)
2. Incidenza annuale di HCC pari al 2,8 % nei pazienti con cirrosi (98) e dello 0,3% nei pazienti senza cirrosi
3. Incidenza cumulativa a 5 e 10 anni di 10 e 14% nei pazienti con cirrosi e di 0,5 e 3,8% nei pazienti senza cirrosi (maschi ed età >50 anni altri fattori di rischio)

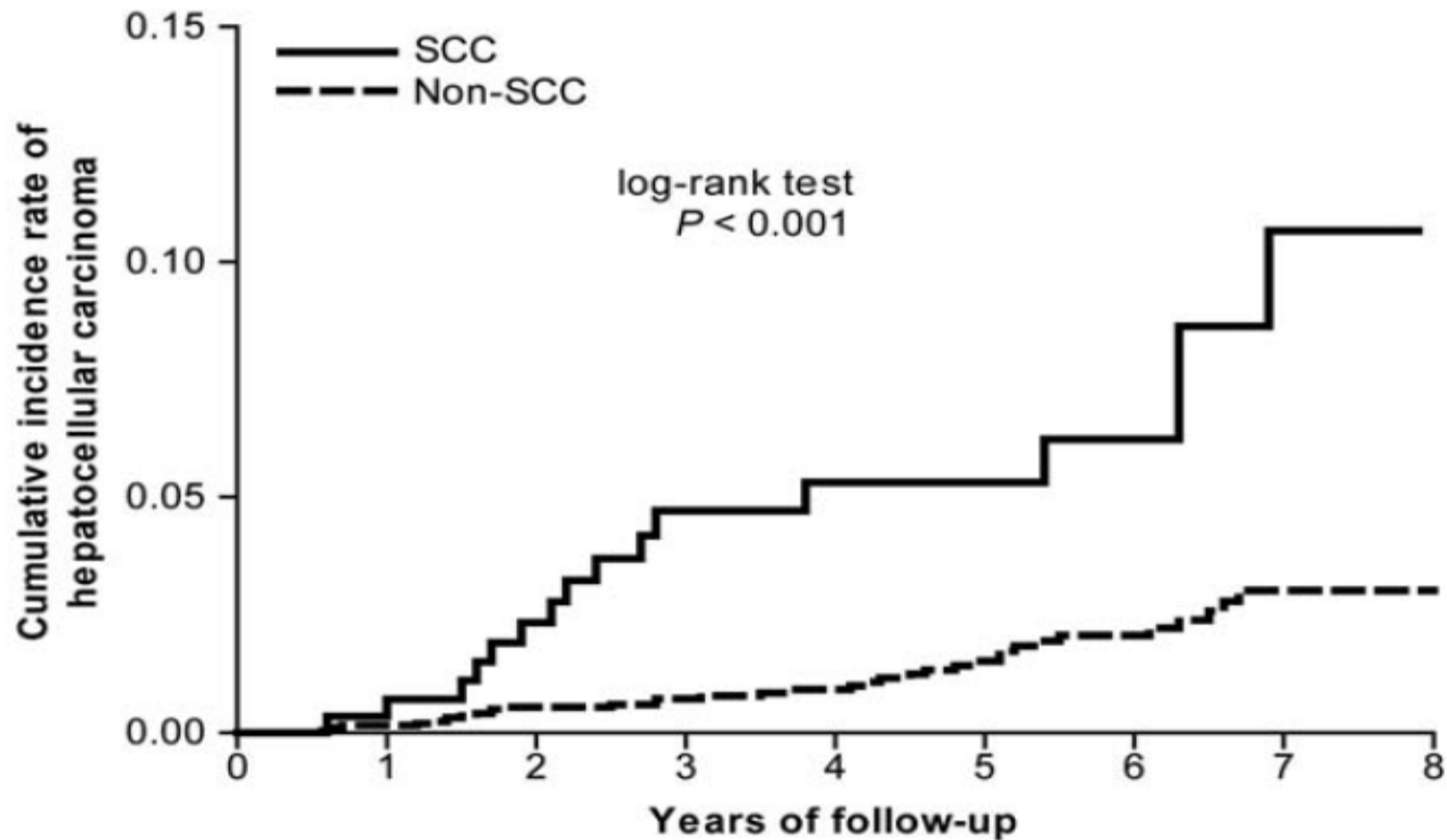
Kim et al J. Hepatol 2015

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Rischio di HCC nei pazienti con cirrosi subclinica da HBV :  
classificazione con Fibroscan ( 285 con kPa > 13 )



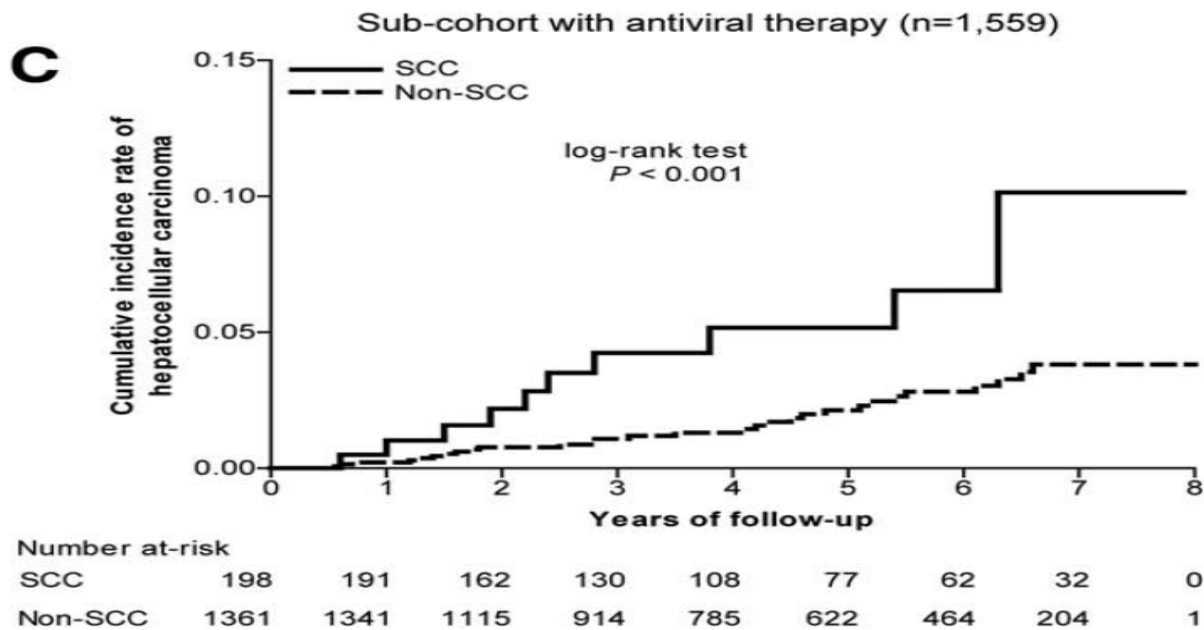
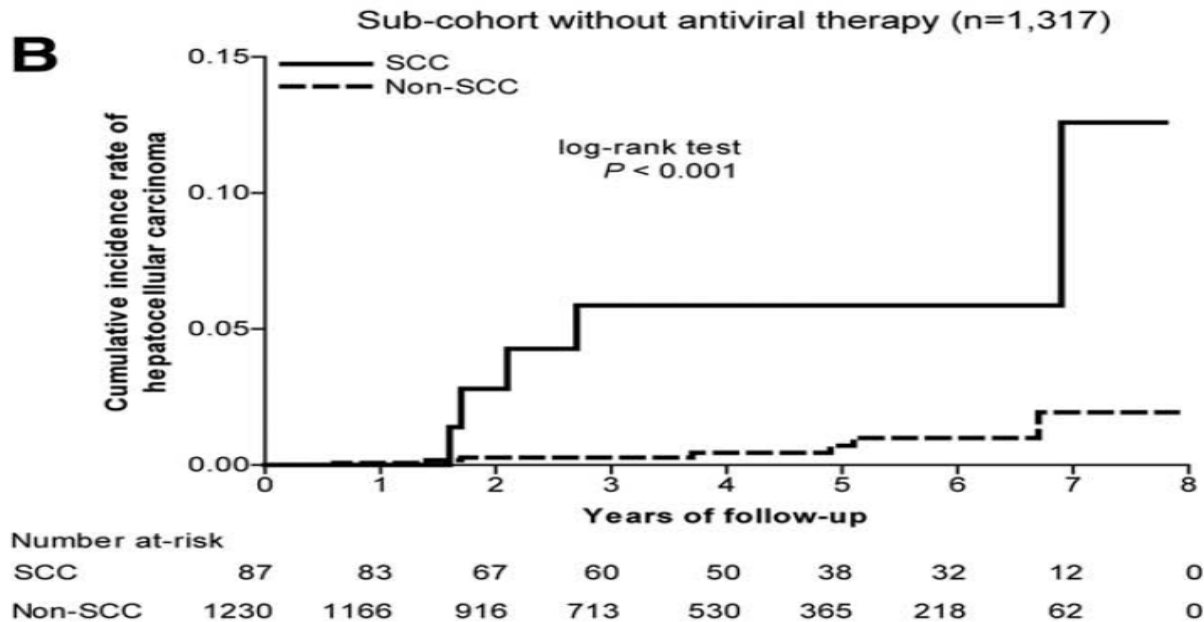
**INCIDENZA DI HCC da HBV : 5,2% vs 1.8 a 5 anni e 13.1 vs 3.9 a 7 anni**



Number at-risk

SCC	285	274	229	190	162	115	94	44	0
Non-SCC	2591	2507	2031	1627	1315	988	683	359	1

# Incidenza di HCC rispetto alla terapia antivirale





## **EASL–EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma**

European Association for the Study of the Liver\*,  
European Organisation for Research and Treatment of Cancer

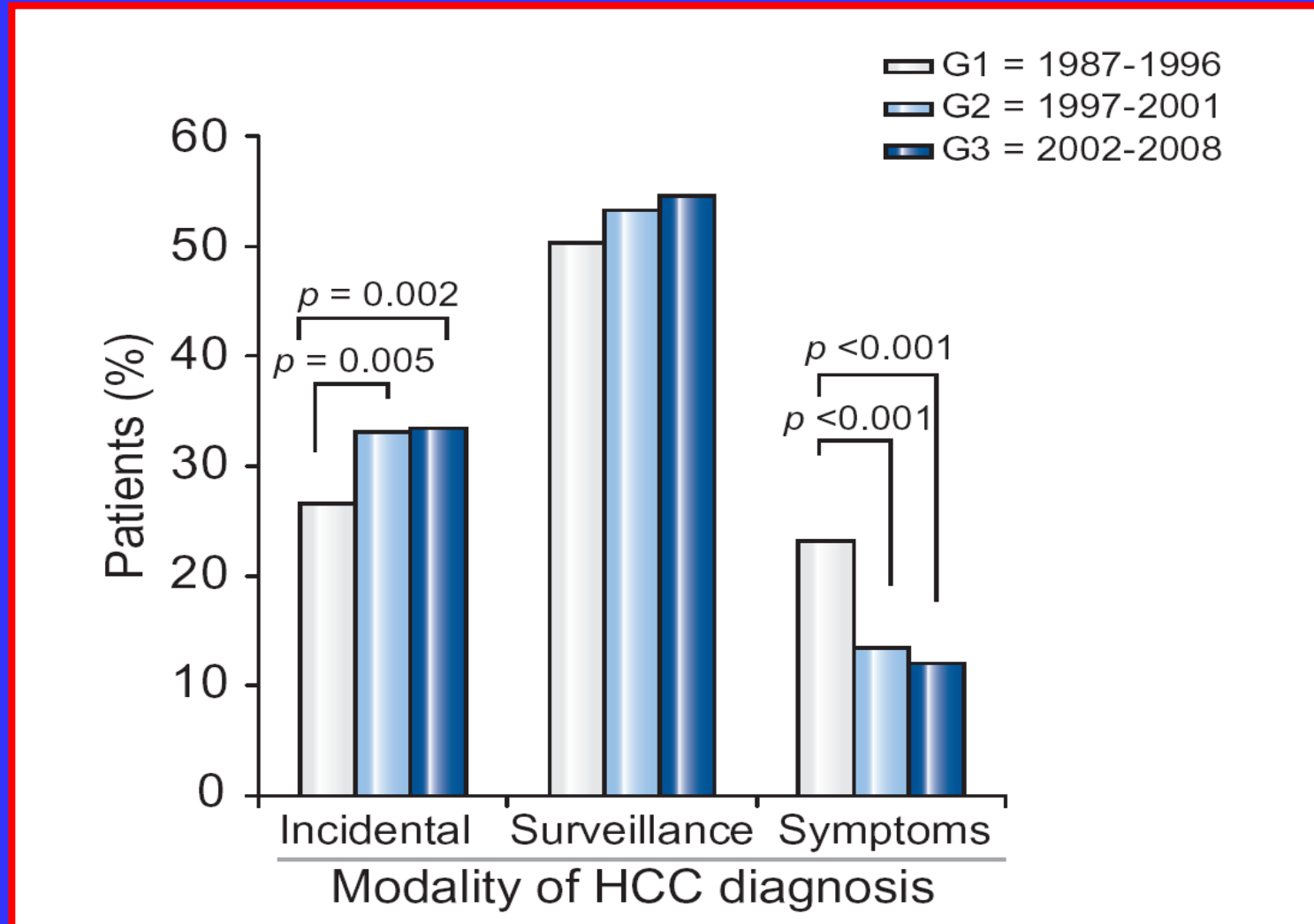
### **SURVEILLANCE**

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

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

A shorter follow-up interval is recommended in : 1. Nodules of less than 1 cm ;  
2. in the follow-up strategy after resection or loco-regional therapies  
( **evidence 3D ; recommendation 2B** )

# Scenario of HCC in Italy : Modality of diagnosis in the three periods

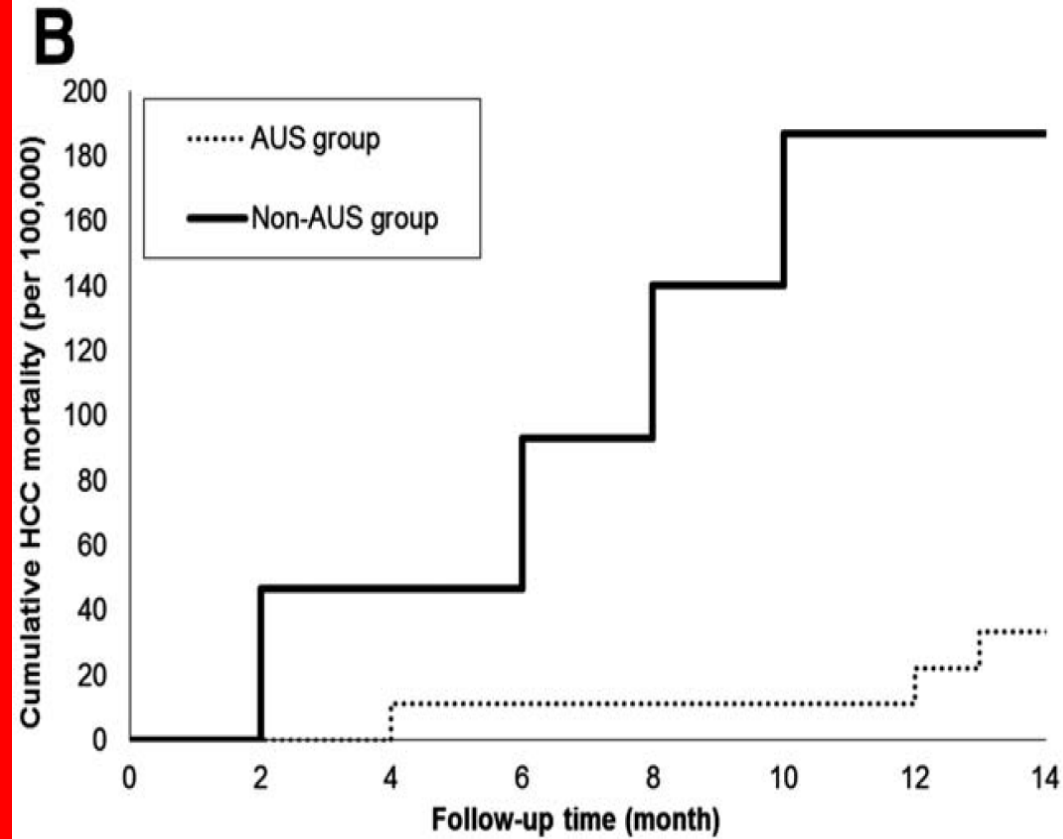
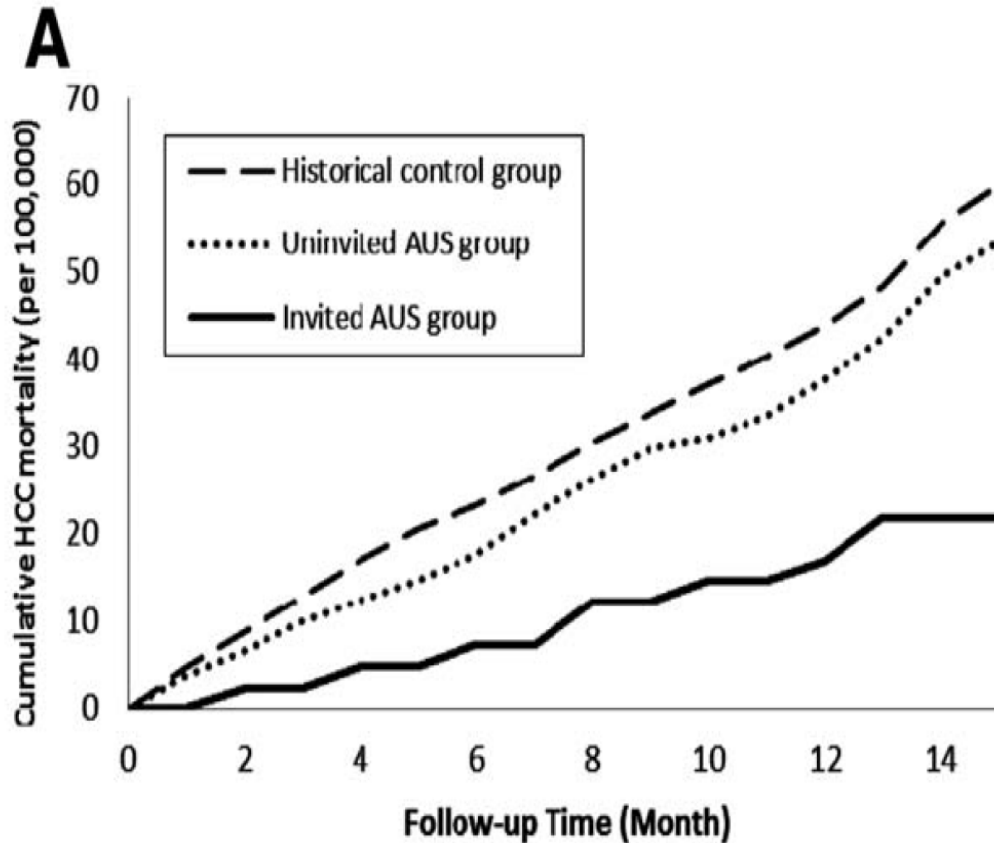


Santi V et al J Hepatology 2012

## Evaluation of abdominal ultrasonography mass screening for hepatocellular carcinoma in Taiwan (Yeh et al .Hepatology , May 2014)

- Invitati 11,114 pazienti di età compresa fra 45 e 69 anni , residenti in un'area ad elevata incidenza per HCC, ad eseguire un esame US secondo un apposito schema " risk score" .
- Fra gli 8.962 che hanno accettato di partecipare ( 80,6%) sono stati identificati 16 HCC screen detected.
- La mortalità cumulativa ( per 100.000) per HCC nel gruppo invitato sottoposto a US ( 17.2) è risultata significativamente inferiore rispetto al gruppo non invitato ( 42,9) e ad un gruppo storico di confronto ( 47,5)

# Confronto fra tassi di mortalità fra popolazione invitata e non invitata allo screening ecografico e un gruppo di controllo storico



# Impatto clinico della diagnosi di HCC

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LA DIAGNOSI : CEUS, TAC  
RMN e biopsia ecoguidata

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## Usefulness of contrast-enhanced perfusional sonography in the assessment of hepatocellular carcinoma hypervascular at spiral computed tomography

Stefano Gaiani<sup>1,\*</sup>, Natascia Celli<sup>1</sup>, Fabio Piscaglia<sup>1</sup>, Laura Cecilioni<sup>1</sup>, Franco Losinno<sup>2</sup>,  
Francesco Giangregorio<sup>3</sup>, Mikaela Mancini<sup>1</sup>, Patrizia Pini<sup>1</sup>, Fabio Fornari<sup>3</sup>, Luigi Bolondi<sup>1</sup>

<sup>1</sup>*Medicina Interna, Dipartimento di Medicina Interna e Gastroenterologia, Alma Mater Studiorum, Università di Bologna,  
via Albertoni 15, 40138 Bologna, Italy*

<sup>2</sup>*U.O. Radiologia, Azienda Ospedaliera S. Orsola-Malpighi, Bologna, Italy*

<sup>3</sup>*U.O. Gastroenterologia, Ospedale Civile, Piacenza, Italy*

**Inclusi dello studio 79 pazienti cirrotici con 103 noduli con ipervascolarità arteriosa alla TAC .**

**La CEUS ha dimostrato una sensibilità del 66,6%, 87,5% , 91,7% e 97,3% per noduli di 1, 1-2, 2-3 e > 3 cm .**

**CEUS utile per la caratterizzazione immediata dei noduli rilevati con la sorveglianza US**

**ESAOTE ACCORSI L** OSP.PC GASTRO  
**B: PEN / DPT 94 mm / G 110**

**Technos MPX**  
 02/09/2007 PB 5  
 05:16:47 AM SCC 10  
 ENH 2

CnTI

DP 32 KPa MI 0.113 TIS 0.0

153/153

00.18.14

60s

D1 C-Capt: Off D2 D3 Chrono Reset D4 Start/Stop D5 Fund D6 Flash

**Technos MPX**  
 02/09/2007 PB 5  
 05:16:39 AM SCC 10  
 ENH 2

CnTI

OSP.PC GASTRO

DP 32 KPa MI 0.113 TIS 0.0

16/153

00.27.00  
00.58

60s

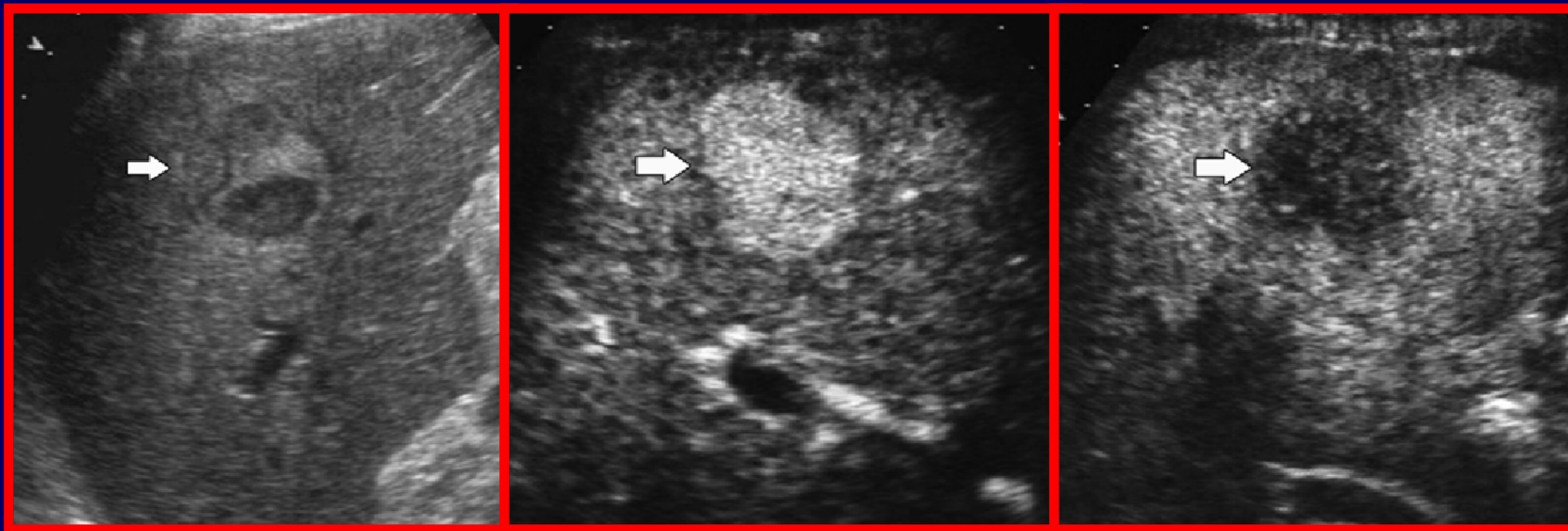
D1 C-Capt: Off D2 D3 Chrono Reset D4 Start/Stop D5 Fund D6 Flash



# Poorly differentiated HCC in cirrhosis related to HCV

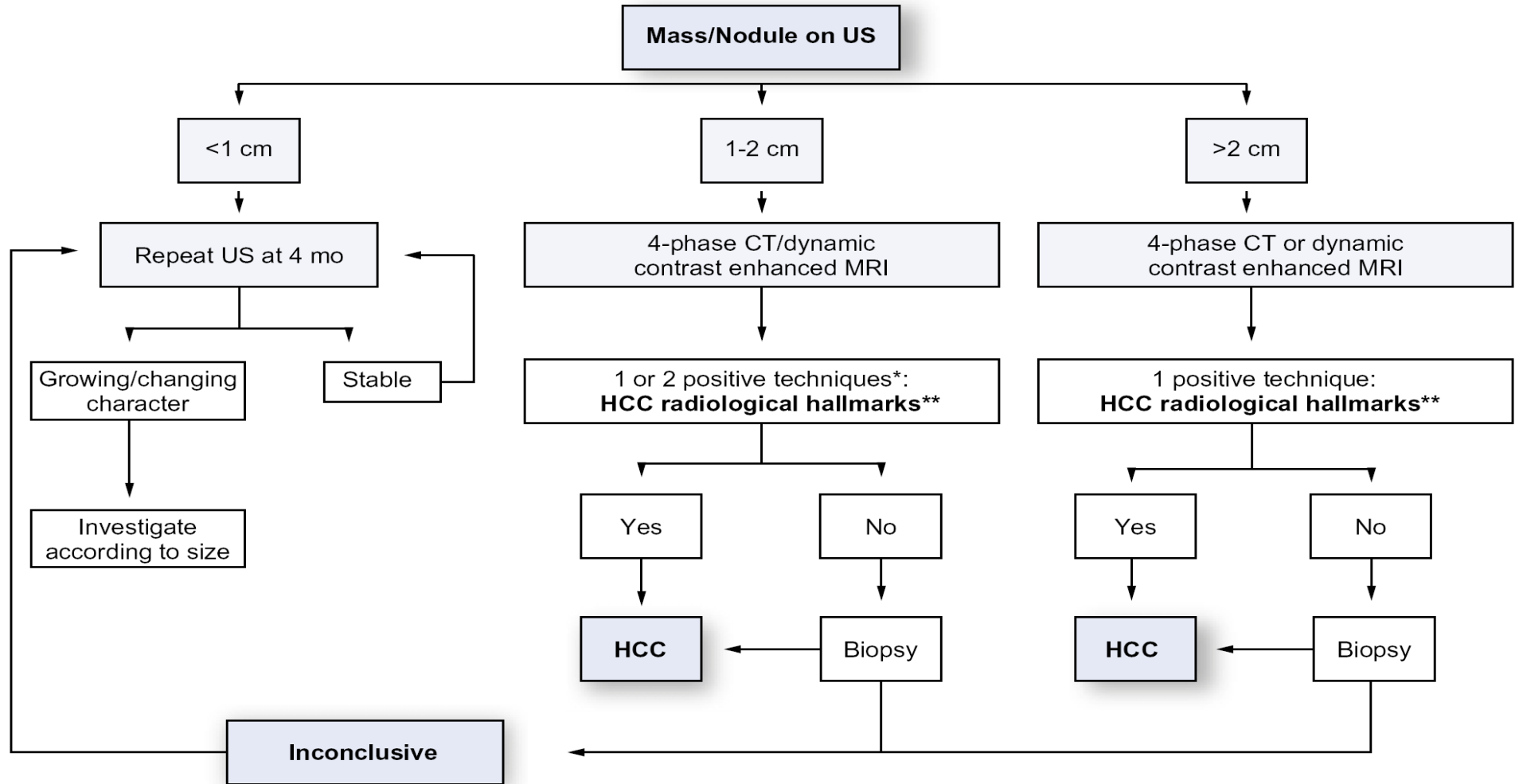
25 sec

Portal phase



Quaia et al AJR 2007

# Diagnostic algorithm and recall policy for HCC





## Clinical and economical impact of 2010 AASLD guidelines for the diagnosis of hepatocellular carcinoma

Matteo Angelo Manini<sup>1</sup>, Angelo Sangiovanni<sup>1,\*</sup>, Fabio Fornari<sup>2</sup>, Fabio Piscaglia<sup>3</sup>, Marco Biolato<sup>4</sup>, Libera Fanigliulo<sup>2</sup>, Elisa Ravaldi<sup>3</sup>, Antonio Grieco<sup>4</sup>, Massimo Colombo<sup>1</sup>,  
on behalf of the Study Participants

<sup>1</sup>A.M. & A. Migliavacca Center for Liver Disease and 1st Division of Gastroenterology, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy; <sup>2</sup>Gastroenterology and Hepatology Unit, "G. da Saliceto" Hospital, Piacenza, Italy; <sup>3</sup>Division of Internal Medicine, "Sant'Orsola Malpighi" Hospital, University of Bologna, Italy; <sup>4</sup>Institute of Internal Medicine, School of Medical, Catholic University of the Sacred Heart, Rome, Italy

**CEUS sensitivity 69% and specificity 100%**  
(CEUS did not detect any HCC typical vascular pattern missed by CT and MRI)

**A sequential study with either CT or MRI enhances the radiological diagnosis of HCC and reduces costs and liver biopsy need . ( 2014 vol. 60 ; 995-1001)**

Clinical and economical impact of 2010 AASLD guidelines for the diagnosis of HCC ( Manini, Sangiovanni , Fornari et al. Milano, Piacenza, Bologna , Roma J Hepatol. 2014 )

- Inclusi nello studio 119 noduli epatici di nuova diagnosi identificati con sorveglianza US in 98 pazienti cirrotici .
- Le dimensioni di noduli erano così suddivise : 7 < 1 cm ; 67 1-2 cm ; 45 > 2 cm ed erano esaminati sequenzialmente con CEUS e TAC , utilizzando la RM solo nei noduli che non presentavano un pattern vascolare tipico . FNB eseguita secondo le linee guida.
- Nel 70% si trattava di HCC . La diagnosi corretta è stata fatta nell'88% dei tumori di 1-2 cm e nel 95% di quelli > 2cm in accordo con i criteri AASLD .
- Rispetto ai criteri 2005 sono state risparmiate 6 FNB con una riduzione dei costi per i noduli > 2 cm .

## HCC typical vascular pattern in 1-2 cm liver nodules

CEUS	Technique		1-2 cm nodule	
	CT	MRI*	No. nodules	No. HCC
+	+	n.n.	23 (35%)	23 (53%)
+	-	+	4 (6%)	4 (9%)
+	-	-	0	0
-	+	-	2 (3%)	2 (5%)
-	+	+	5 (7%)	5 (12%)
-	-	+	4 (6%)	4 (9%)
-	-	-	29 (43%)	5 (12%)
<b>Total</b>			67 (100%)	43 (100%)

## HCC typical vascular pattern in > 2 cm liver nodules

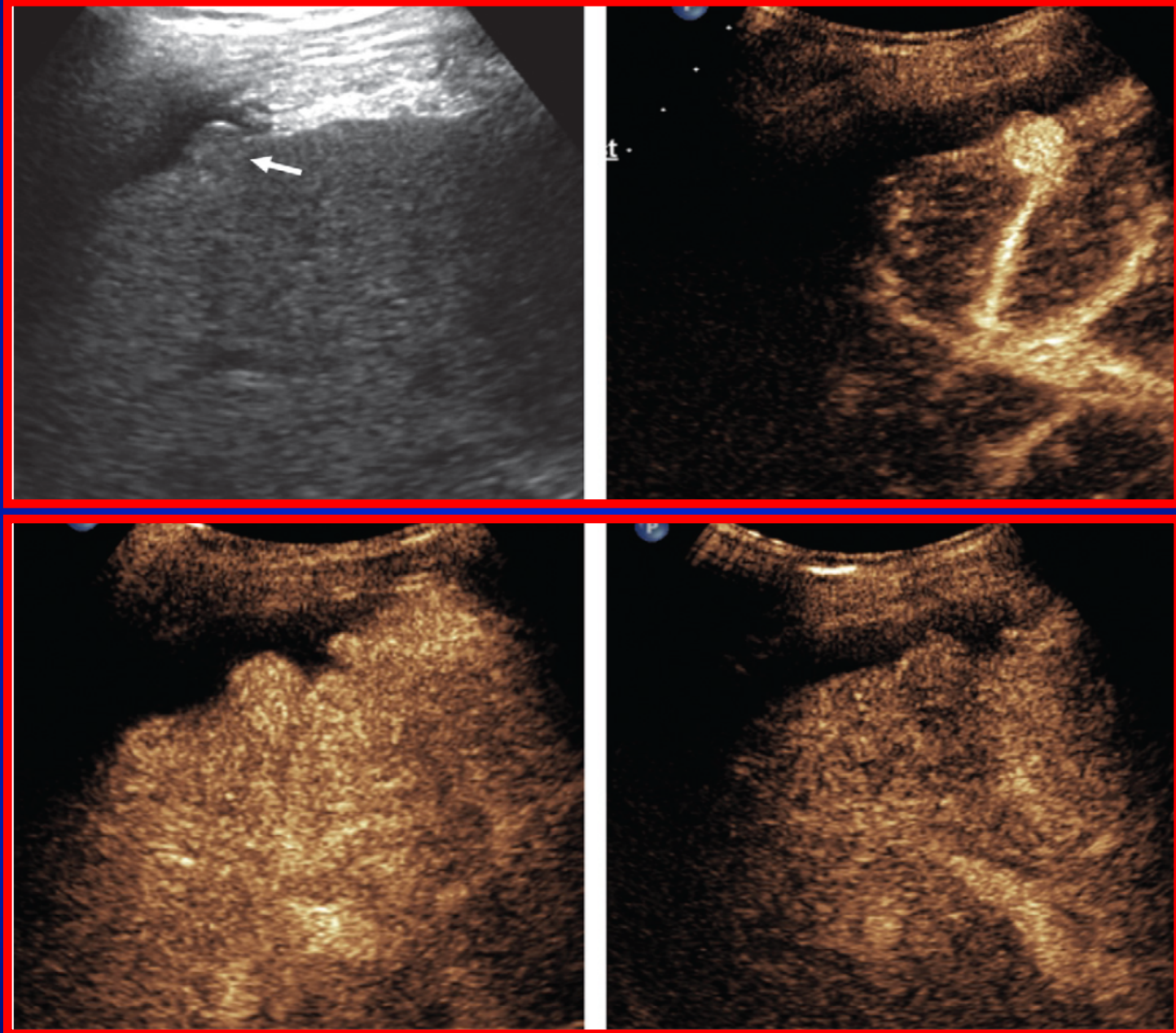
CEUS	Technique		>2 cm nodule	
	CT	MRI*	No. nodules	No. HCC
+	+	n.n.	30 (66%)	30 (75%)
+	-	+	1 (2%)	1 (3%)
+	-	-	0	0
-	+	n.n.	7 (16%)	7 (17%)
-	-	+	0	0
-	-	-	7 (16%)	2 (5%)
<b>Total</b>			45 (100%)	40 (100%)

Lack of arterial hypervascularity at CEUS should not define the priority for diagnostic work-up of nodules < 2 cm

- ✦ Inclusi nello studio 168 pazienti con un nodulo epatico solitario del diametro di < 20 cm esaminati con CEUS e MRI .
- ✦ Diagnosi finale di HCC in 119 ; 3 iCC; 1 metastasi; 45 lesioni benigne di cui 35 MRNs
- ✦ I noduli di HCC presentavano un diametro maggiore ( 16 vs 12 mm) .
- ✦ 55 noduli ( di cui 18 HCC) privi di contrast-enhancement arterioso alla CEUS
- ✦ L'assenza di contrast-enhancement arterioso alla CEUS nei noduli < 2 cm non esclude la diagnosi di HCC

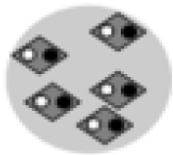
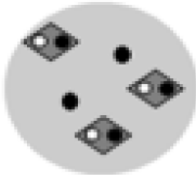

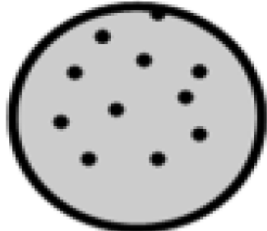




# Images of small superficial HCC





# International Consensus on small nodular lesions in cirrhotic liver

				
<b>IWP classification</b>	L-DN	H-DN	WD-HCC	MD-HCC
<b>Pathological features</b>				
gross appearance			vaguely-nodular	distinctly-nodular
stromal invasion	(-)	(-)	+ / -	+ / -
<b>Clinical (imaging)</b>				
arterial supply	iso / hypo	iso / hypo	iso / hypo rarely hyper	hyper
portal vein supply	+	+	+	-
<b>Clinico-pathological</b>	Premalignant		Early HCC	Progressed HCC
	 Intratumoral portal tract	 Unpaired artery		
	H-DN: High grade dysplastic nodule L-DN: Low-grade dysplastic nodule WD: Well-differentiated MD: Moderately differentiated iso: isovascular hypo: hypovascular hyper: hypervascular			

## EVALUATION OF CEUS FOR DIAGNOSIS OF DYSPLASTIC NODULES WITH A FOCUS OF HCC IN CIRRHOSIS

193 pazienti con cirrosi epatica inclusi nello studio .

215 lesioni focali epatiche di diametro variabile da 1 a 3,5 cm .

La diagnosi finale : 86 HCC; 102 RN e 27 DN-HCC .

**Alla CEUS :**

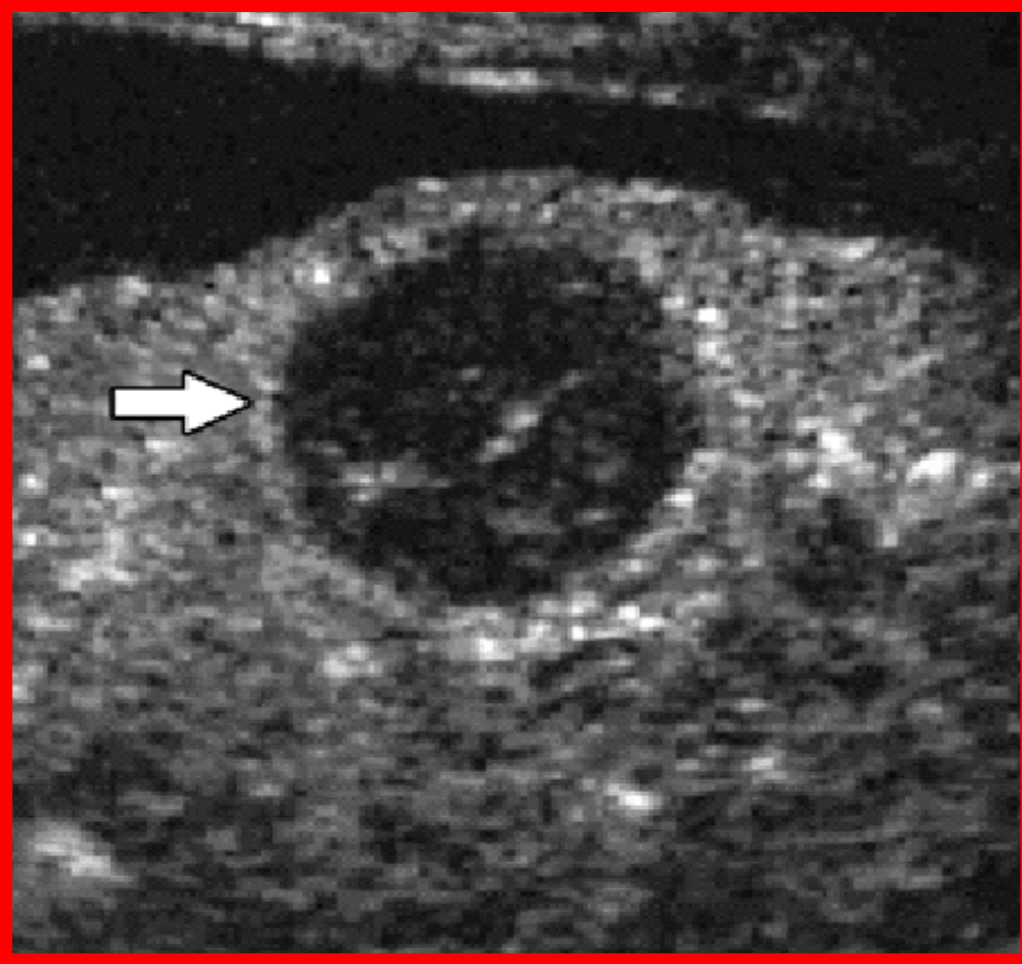
HCC con enhancement arterioso nell'87,2% e 100% wash-out;  
RN nel 73,5% assenza di wash-out ;

DN-HCC enhancement e wash-out solo parziale

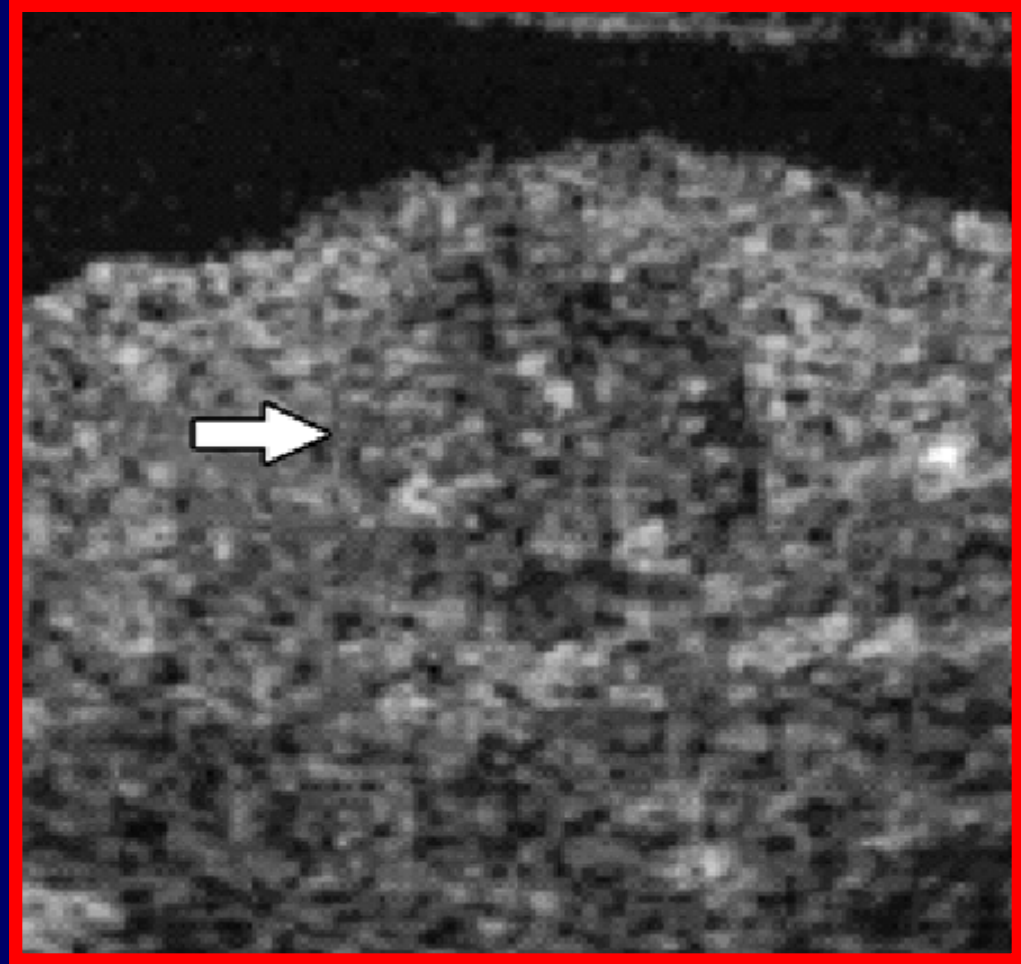
**CEUS ausilio importante per valutare la progressione da RN a DN a HCC . Utile anche per la guida della biopsia**

# Regenerative nodule in cirrhosis related to HBV

25 sec

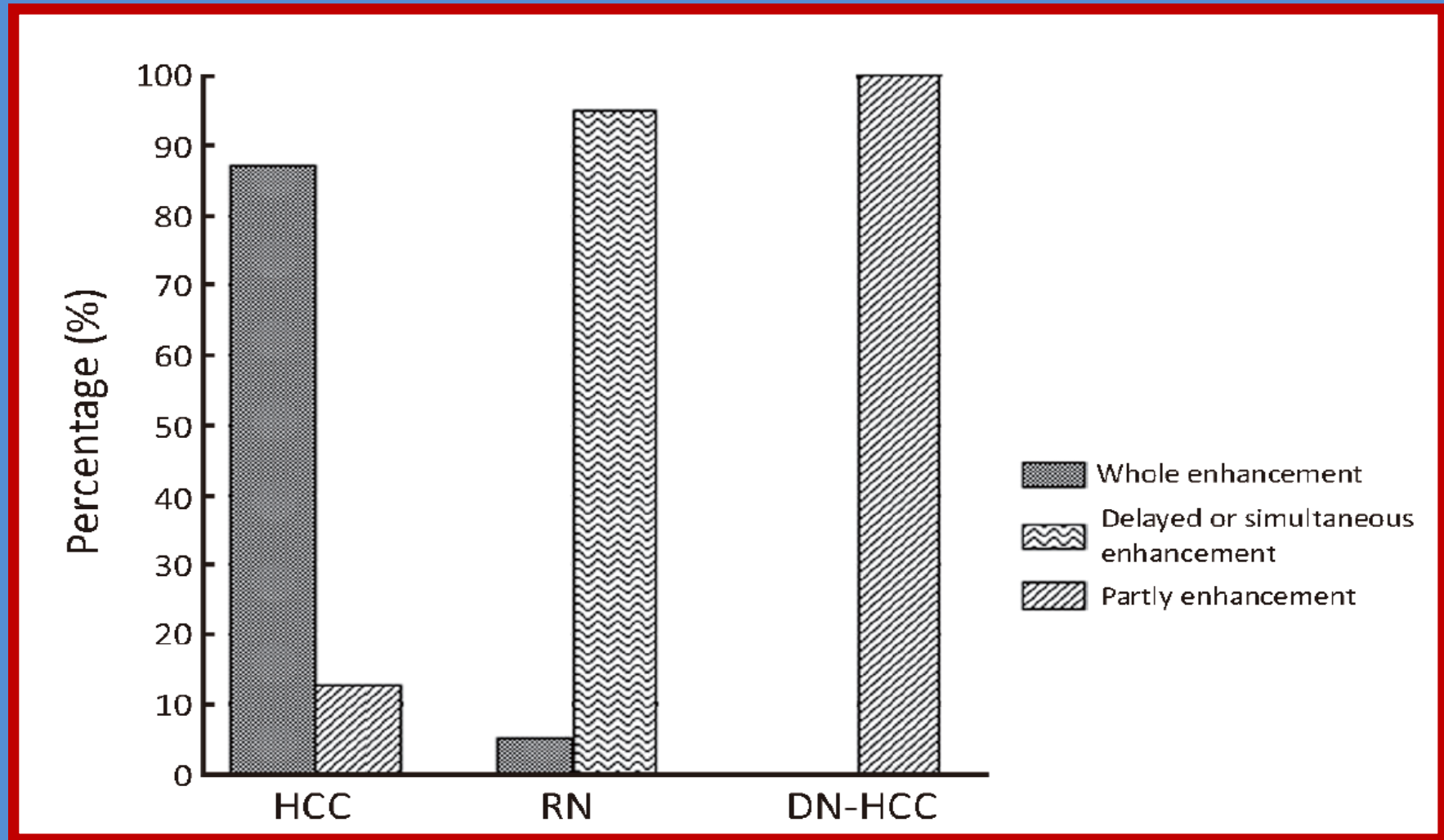


150 sec



Quaia et al AJR 2007

## Aspetto di HCC , RN e DN-HCC nella fase arteriosa di CEUS



## **New imaging techniques for liver diseases**

Bernard E. Van Beers\*, Jean-Luc Daire, Philippe Garteiser

*Laboratory of Imaging Biomarkers, UMR1149 INSERM-University Paris Diderot, Sorbonne Paris Cité, Department of Radiology,  
Beaujon University Hospital Paris Nord, Clichy, France*

Dynamic CEUS has the potential to give similar diagnostic performance for single liver tumour assessment as dynamic contrast-enhanced MR imaging and can provide quantitative perfusion information.

Problematiche : la diagnosi del CC intraepatico ; difficoltà di standardizzazione ; operatore-dipendente ; variabilità dei risultati.

Punti a favore : fase vascolare precoce dell'HCC; costo-efficacia superiore a TAC e MRI con performance diagnostica analoga

Prospettive future : quantitative perfusion imaging e molecular imaging

# Impatto clinico della diagnosi di HCC

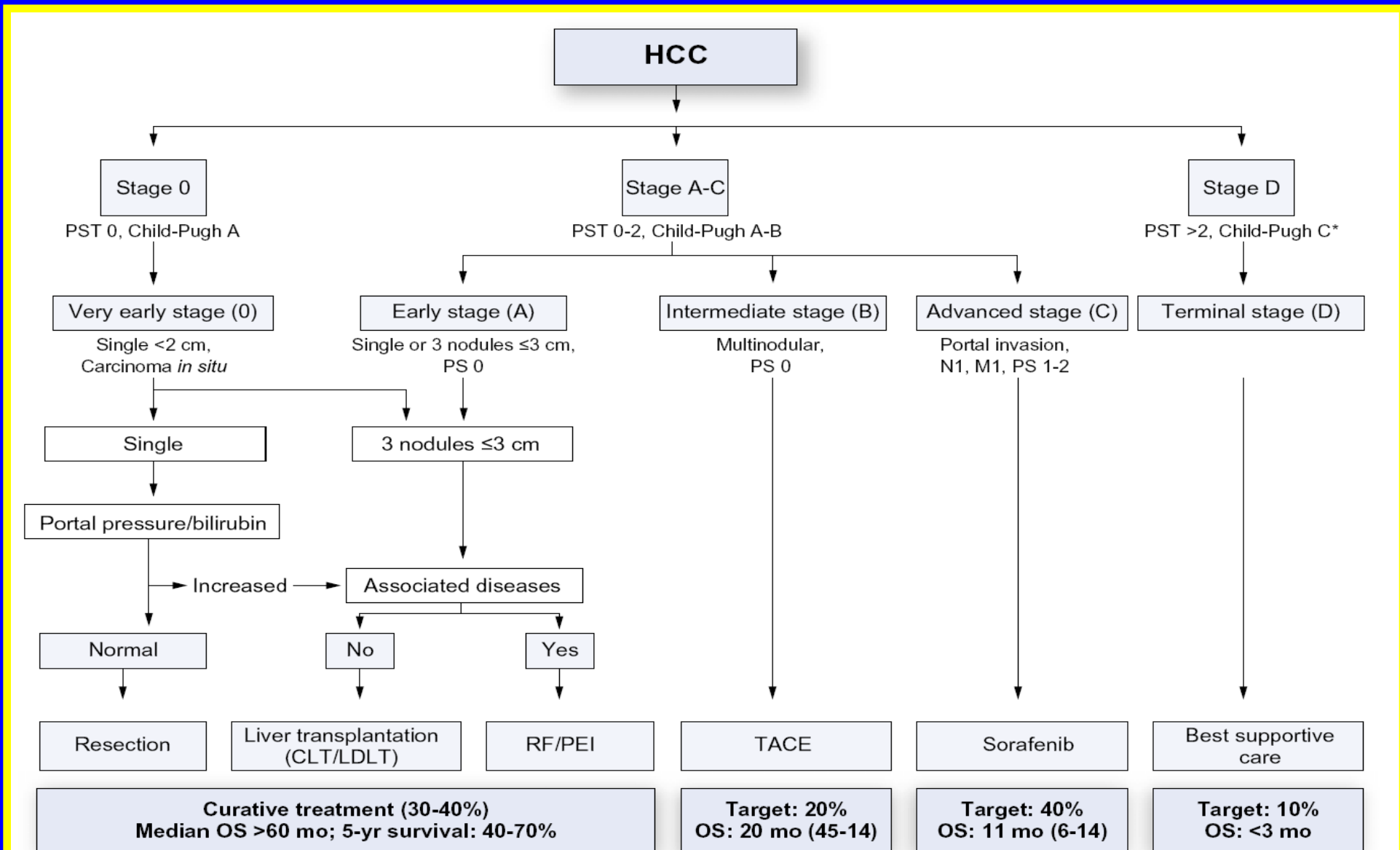
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Le scelte terapeutiche nella fase iniziale

Le scelte terapeutiche nella malattia avanzata

---

# Updated BCLC staging system and treatment strategy





**Scenario of HCC in Italy : treatments  
( age of the 3027 HCC patients: 68 years)**

	n (%)	1987-1996 G1 (%)	1997-2001 G2 (%)	2002-2008 G3 (%)
Treatment	2907 (96)			
OLT	63 (2.2)	17 (2.3)	14 (1.7)	32 (2.4)
Resection	300 (10.3)	70 (9.4)	87 (10.3)	143 (10.9)
Percutaneous ablation	772 (26.6)	155 (20.7)	224 (26.6)	393 (29.8)
TACE <sup>+</sup>	917 (31.5)	250 (33.4)	271 (32.2)	396 (30.1)
Others*	855 (29.4)	256 (34.2)	246 (29.2)	353 (26.8)

**Santi V et al J Hepatology 2012**

## Adherence to AASLD guidelines for management of HCC : an italian prospective multicenter in-field study

Inclusi nella casistica tutti i nuovi casi di HCC osservati consecutivamente per un periodo di 34 mesi in 30 ospedali Italiani ( 536 pazienti) ; 53,9% da sorveglianza ecografica periodica.

Età media 70 anni ( 53% > 70 anni) ; 71% maschi ; presenza di comorbidità nel 74% ( nel 31% di grado severo) ; Child A 63%; BCLC A 55%; BCLC B 22%.

Nel 18% presenza di HCC del diametro < 2 cm ; nel 54% HCC singolo.

I pazienti con BCLC 0-A sono stati sottoposti alle seguenti terapie :

Trapianto epatico nel 2% ; Resezione chirurgica nell' 8,8% ;

Ablazione percutanea nel 48,8% ; TACE nel 25,7% ; altre nel 4,7%.

## **EASL–EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma**

European Association for the Study of the Liver\*,  
European Organisation for Research and Treatment of Cancer

### **TREATMENT**

Resection is the first line treatment option for patients with solitary tumors and very well- preserved liver function (evidence 2 A; recommendation 1B).

Liver transplantation is considered to be the first-line treatment option for patients with single tumor less than 5 cm or < 3 nodules < 3 cm ( Milan criteria) not suitable for resection ( evidence 2A; recommendation 1 A) .

Neo-adjuvant treatment can be considered for loco-regional therapies if the waiting list exceeds 6 months ( evidence 2D ; recommendation 2B )

# Predicting Survival after Liver Transplantation in Patients with HCC beyond Milan Criteria

	No. of Patients (n=1556)	Milan in (n=444)	Milan out (n=1112)	P-value
No. tumors Median (range)	3 (1-20)	1 (1-3)	4 (1-20)	<0.0001
Max tumor size, mm Median (range)	35 (1-200)	20 (1-50)	40 (4-200)	<0.0001
Vascular invasion, n				
No	977 (66.2%)	361 (89.1%)	616 (57.6%)	<0.0001
Yes	498 (33.8%)	44 (10.9%)	454 (42.4%)	
Overall survival (95% CI) at 10 years	46.8% (43.0-50.5)	69.6% (63.7-74.8)	38.7% (34.2-43.1)	<0.0001

## Resezione del piccolo HCC ( < 2 cm )

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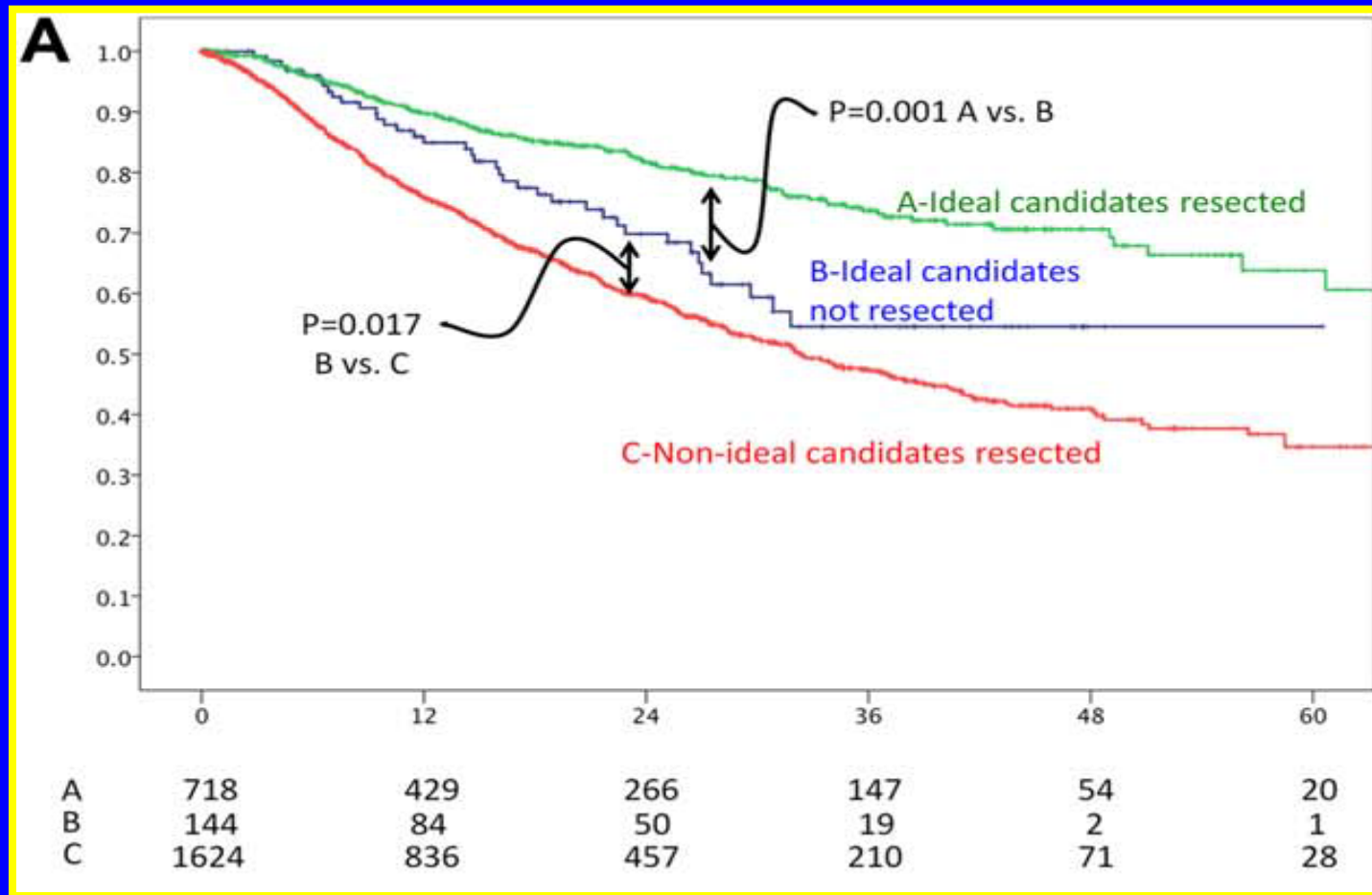
1. Lo studio ha raccolto 132 pazienti con un follow-up di 37.5 mesi (MSMC : New York ; INT : Milano)
  2. Sono stati osservati 32 decessi con una sopravvivenza media di 74.5 mesi e una sopravvivenza a 5 anni del 70%.
  3. Il tempo medio per la recidiva è stato di 31.6 mesi e la percentuale di recidiva a 5 anni è stata del 68% .
  4. La resezione chirurgica dovrebbe essere ancora oggi considerata la terapia di prima scelta ( Roayale et al . Hepatology , 2013)
-

# La resezione chirurgica del piccolo HCC (< 2 cm ) :132 pazienti

Variable	<i>P</i>	HR (95% CI)
Survival		
Satellites present	0.031	2.46 (1.08-5.62)
Platelets <150,000/ $\mu$ L	0.026	2.37 (1.07-5.24)
Overall recurrence		
Satellites present	0.003	2.79 (1.42-5.46)
Cirrhosis (fibrosis 4)*	0.010	2.30 (1.22-4.34)
Nonanatomic resection	0.031	1.79 (1.06-3.07)
Very early recurrence ( $\leq$ 1 year)		
Nonanatomic resection	0.010	3.39 (1.33-8.62)
Tumor size $\geq$ 15 mm	0.004	3.83 (1.55-9.45)
Satellites present	0.011	3.30 (1.31-8.41)
Early recurrence ( $\leq$ 2 years)		
Tumor size $\geq$ 15 mm	0.021	2.39 (1.14-5.01)
Poor differentiation	0.030	2.40 (1.09-5.29)
Cirrhosis (fibrosis 4)*	0.020	3.40 (1.16-9.38)

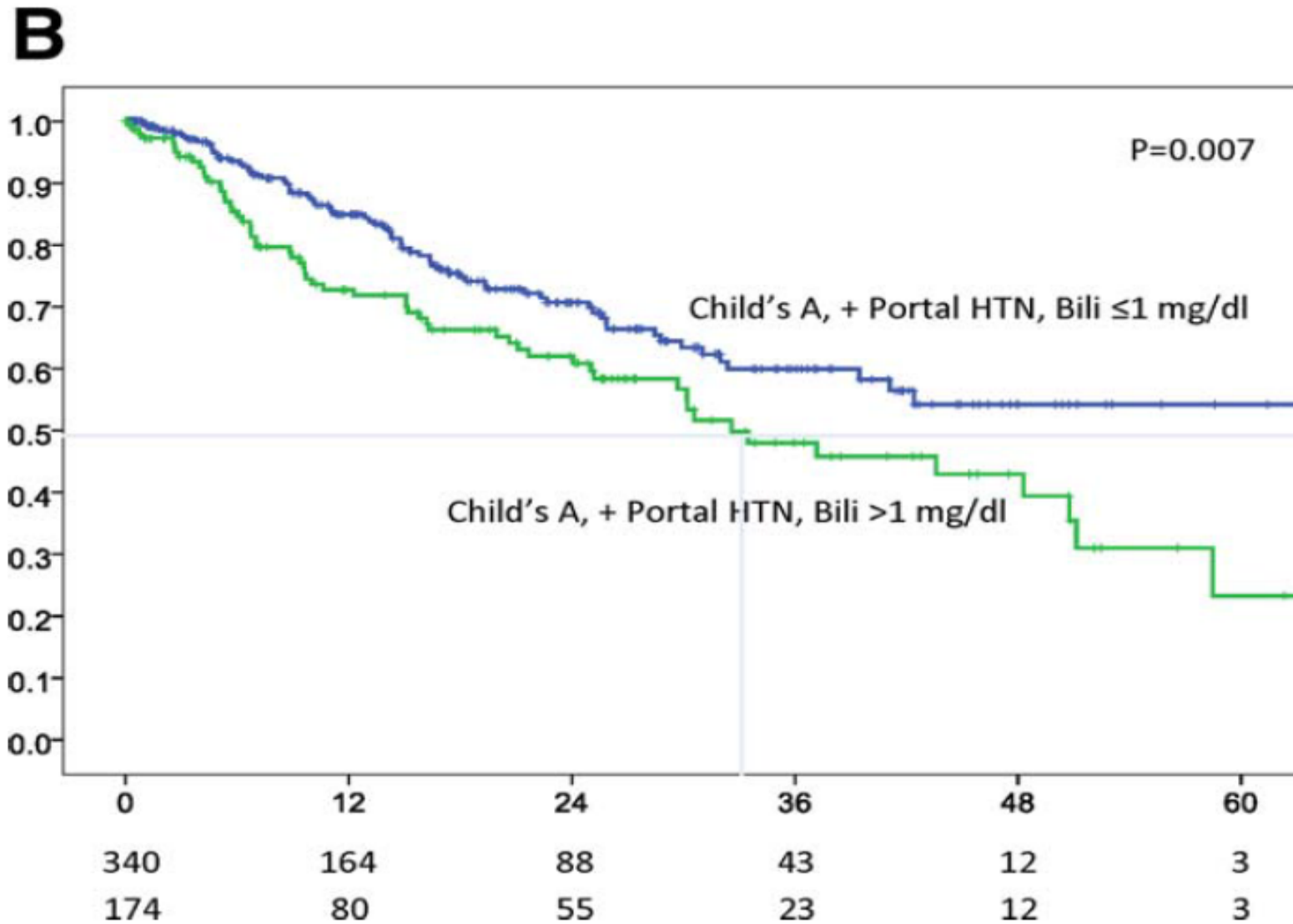
\*Metavir score.

# Il ruolo della resezione epatica nel trattamento dell'HCC: 8.656 pazienti in 20 centri

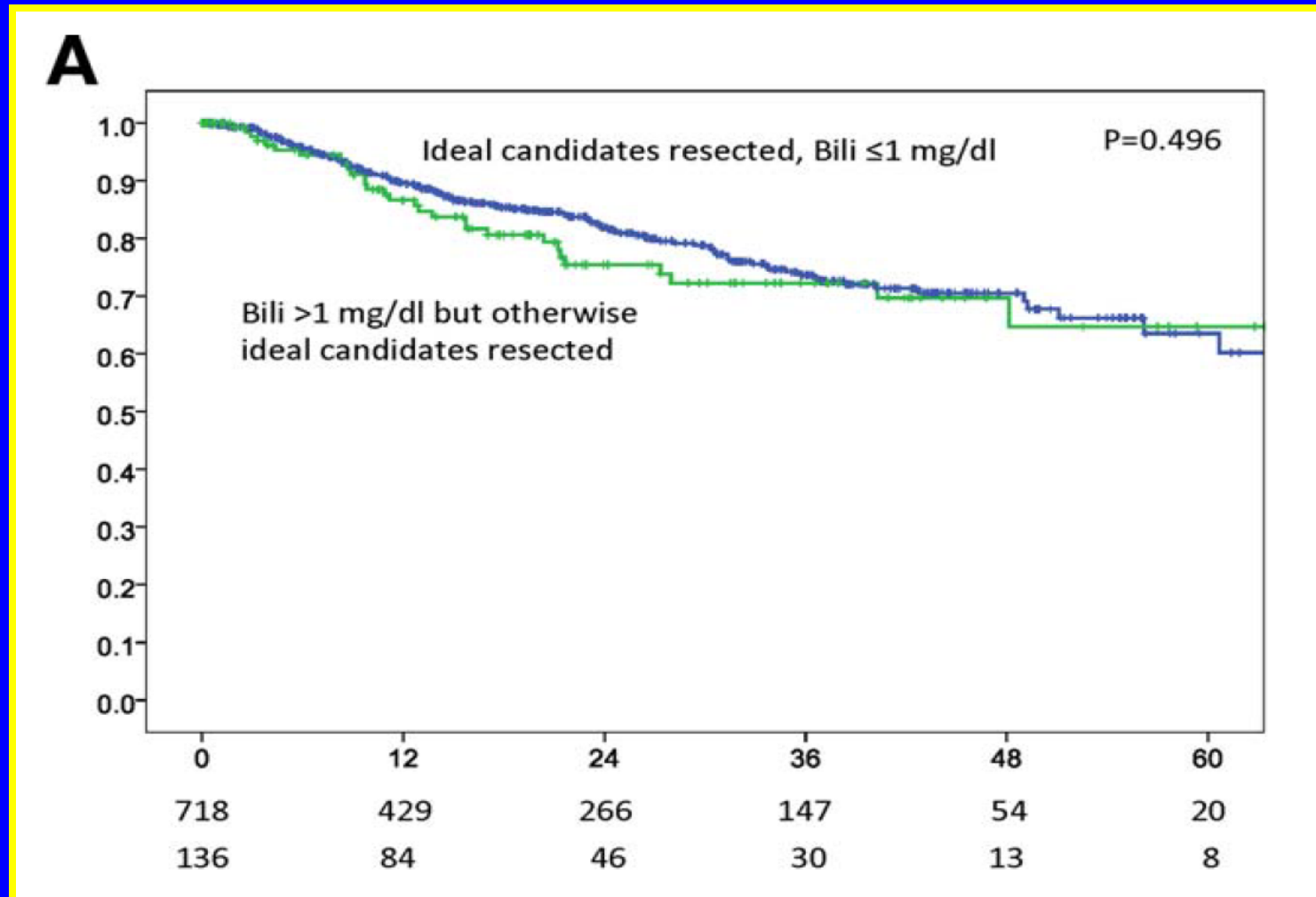




# La resezione epatica nell'HCC : stratificazione per ipertensione portale



# Il ruolo della resezione epatica nell'HCC : stratificazione per valori di bilirubina



## Il ruolo della resezione epatica nell'HCC : analisi multivariata della sopravvivenza nei candidati non ideali

	<b>Hazard Ratio</b>	<b>95% Confidence Interval</b>	<b>P Value</b>
Age >70 years	1.2237	1.119-1.369	<0.001
Multiple tumors	1.034	0.954-1.119	0.416
PH	1.156	1.068-1.2751	<0.001
AFP >400 ng/mL	1.515	1.398-1.642	<0.001
Tumor size >3 cm	1.770	1.597-1.961	<0.001
BCLC stage (reference = A)			
B	1.431	1.039-2.019	0.039
C	2.4319	1.905-2.823	<0.001
D	5.612	4.272-7.371	<0.001
Treatment (reference = resection)			
Embolization	1.431	1.271-1.611	<0.001
Ablation	0.849	0.737-0.979	0.022
Transplant	0.195	0.141-0.272	<0.001
Other	1.784	1.358-2.344	<0.001

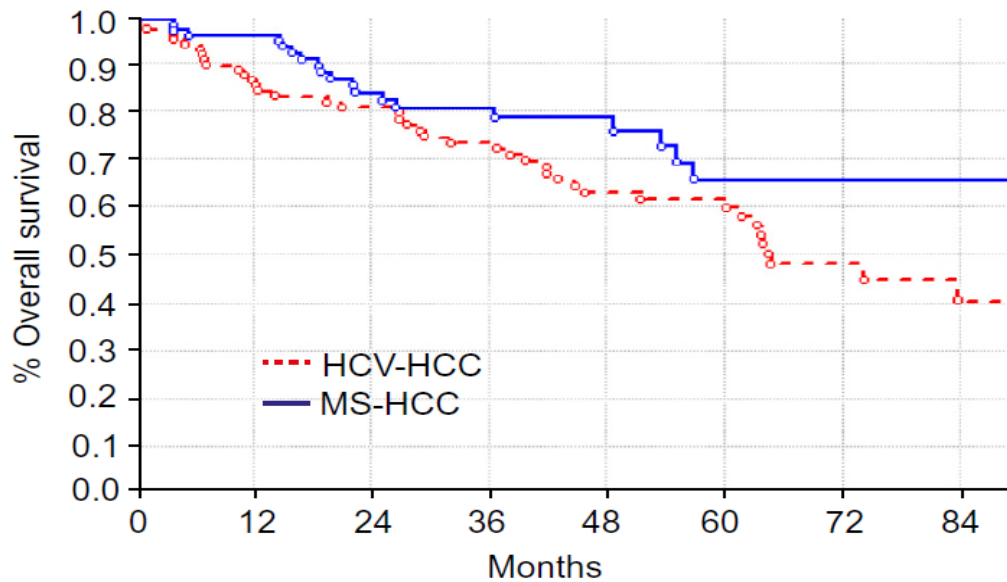
# Caratteristiche cliniche dei pazienti con HCC e sindrome metabolica (SM)

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1. Studio retrospettivo multicentrico italiano che ha raccolto 96 pazienti con HCC e SM confrontati con 96 HCC HCV-correlati sottoposti a resezione epatica
2. Nei pazienti con SM era più elevata la prevalenza di NASH che però non condizionava l'evoluzione
3. Il gruppo SM presentava una migliore sopravvivenza a 5 anni ( 65% vs 61%) e una migliore sopravvivenza libera da recidiva ((37 vs 27% )

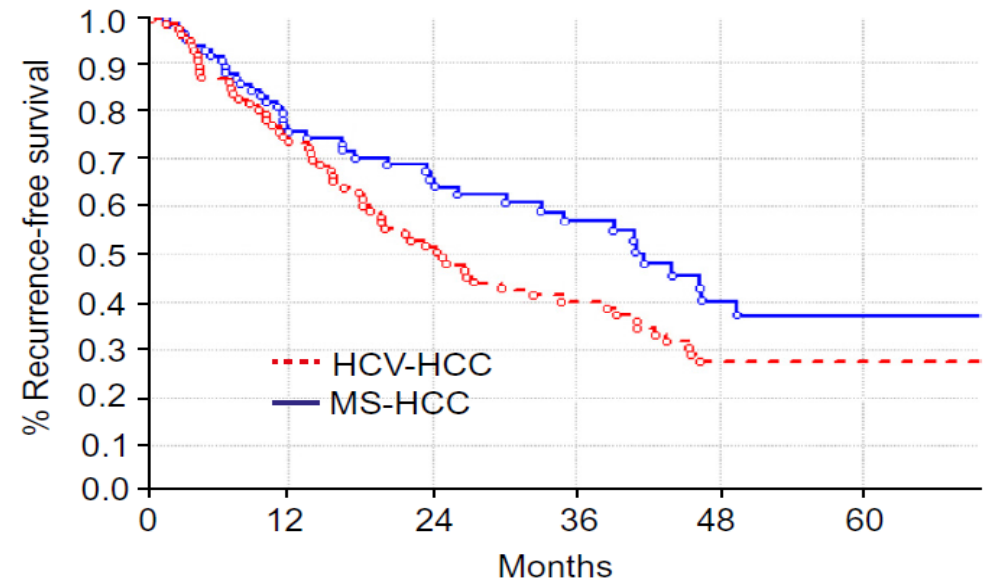
# Resezione epatica per HCC in pazienti con sindrome metabolica

## Sopravvivenza globale



Pts at risk	Total	1 yr	2 yr	3 yr	4 yr	5 yr	6 yr	7 yr
MS-HCC	96	78	55	42	29	18	12	9
HCV-HCC	96	80	69	58	45	36	17	9

## Sopravvivenza libera da recidive



Pts at risk	Total	1 yr	2 yr	3 yr	4 yr	5 yr
MS-HCC	92	61	41	29	14	10
HCV-HCC	92	64	42	30	19	14

# Resezione epatica per HCC in pazienti con sindrome metabolica

	Patients with MS-HCC n = 96 n (%)	Patients with HCV-HCC n = 96 n (%)	p value
<b>Demographic data</b>			
Age, years	71 (40-84)	69 (46-84)	0.243
Age >70 years	50 (52.1)	42 (43.8)	0.248
Male sex	82 (85.4)	71 (74.0)	0.049*
BMI >30 kg/m <sup>2</sup>	49 (51.0)	3 (3.1)	<0.001
Arterial hypertension	90 (93.8)	34 (35.4)	<0.001
Diabetes	82 (85.4)	20 (20.8)	<0.001
Dyslipidemia	81 (84.4)	13 (13.5)	<0.001
Hepatitis B infection	-	17 (17.7)	<0.001
<b>Liver function</b>			
Child-Pugh class A	96 (100)	96 (100)	1 (matched)
MELD score	7 (6-16)	7 (6-12)	0.301
Total bilirubin, mg/dL	0.6 (0.2-2.9)	0.67 (0.3-1.9)	0.728
AST, IU/L	30 (12-200)	47.5 (12-410)	<0.001
ALT, IU/L	33 (8-162)	57 (10-383)	<0.001
GGT, IU/L	72.5 (14-516)	65 (13-723)	0.502
INR	1.06 (0.81-1.70)	1.04 (0.89-1.26)	0.131
Albumin, g/dL	4 (3.1-5.5)	3.9 (2.9-5.4)	0.274
Creatinine, mg/dL	0.91 (0.51-1.93)	0.89 (0.43-1.40)	0.102
Platelet count, x10 <sup>3</sup> /mL	204.5 (60-446)	183.5 (53-452)	0.100
ICG test	8.3 (0.1-33.0)	5.7 (0.3-21.7)	0.213
Portal hypertension	7 (7.3)	7 (7.3)	1 (matched)

## **EASL–EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma**

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### **LOCAL ABLATION**

Local ablation with radiofrequency or percutaneous ethanol injection is considered the standard of care for patients with BCLC O-A tumors not suitable for surgery (**evidence 2A; recommendation 1B**).

Radiofrequency ablation is recommended in most instances as the main ablative therapy in tumors less than 5 cm due to a significantly better control of the disease (**evidence 1D; recommendation 1 A**) .

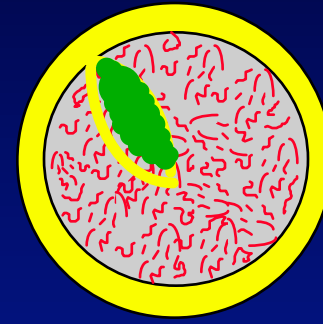
In tumors < 2 cm BCLC O both techniques achieve complete response in more than 90% of cases with good long-term outcome : Wheter they can be considered as competitive alternatives to resection in uncertain (**evidence 1/A ; recommendation 1 C**)



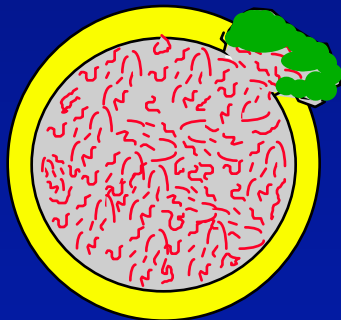
# PEI nell'HCC: Fattori limitanti



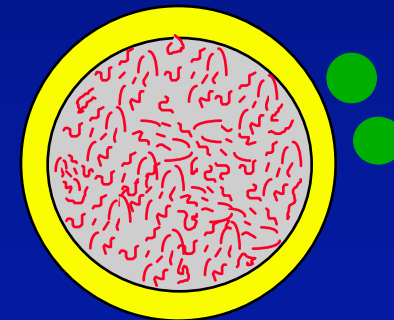
Persistenza periferica



Setti intratumorali

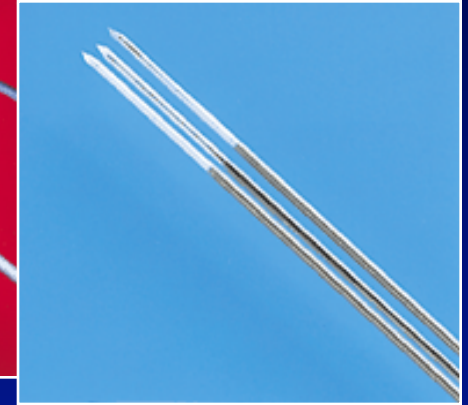
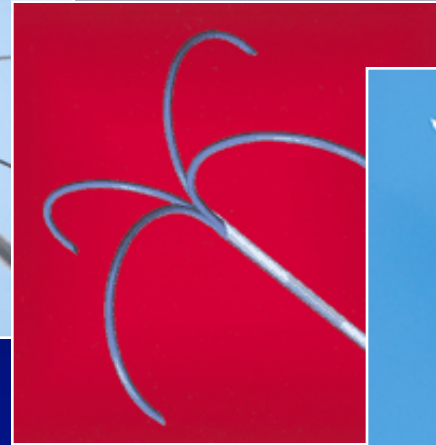
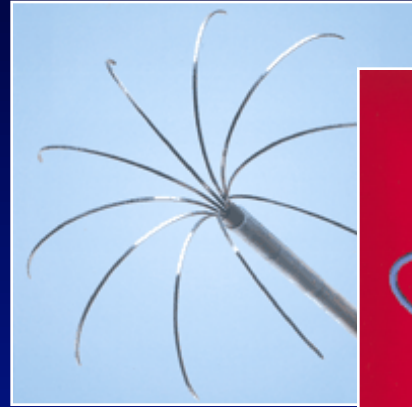


Invasione extracapsulare



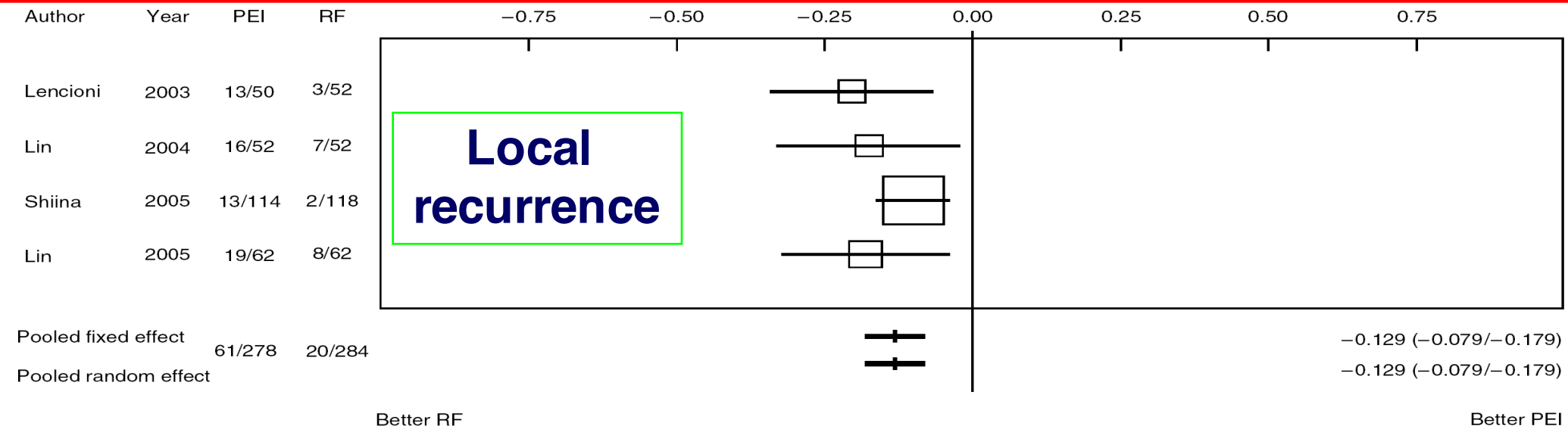
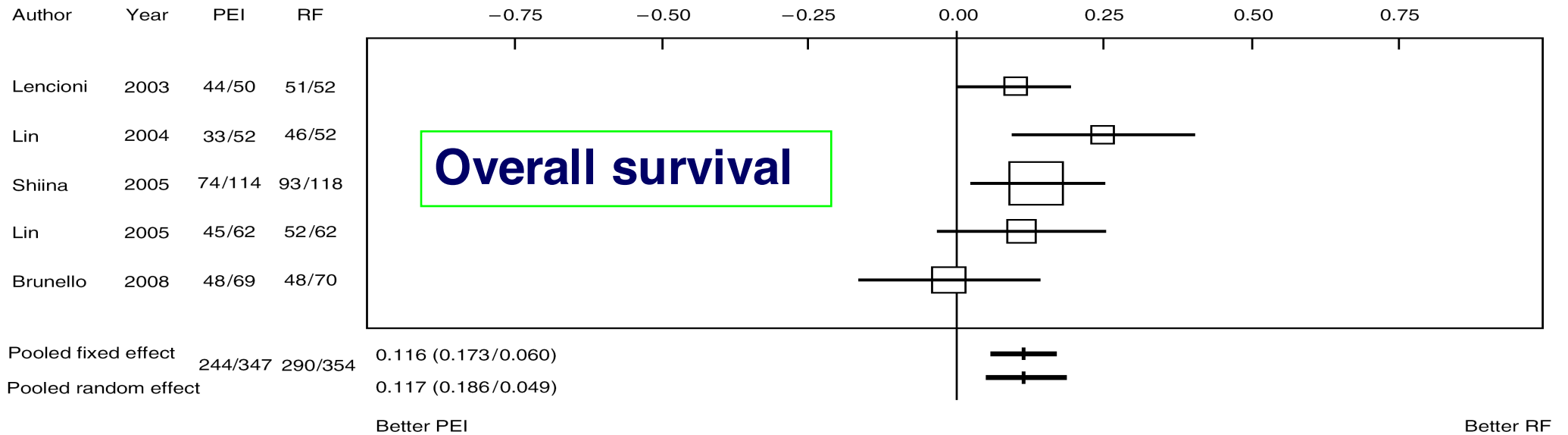
Noduli satelliti

# Technical advances in RFTA



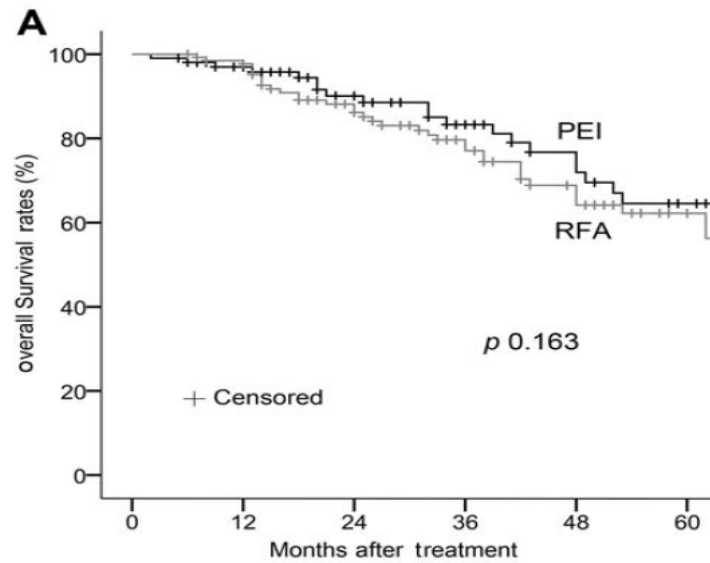
- High-power RF generators (150-200 W)
- Modified electrode needles:
  - Cooled-tip electrodes (single, cluster)
  - Expandable (hooked) electrodes

# RFTA Vs. PEI for small HCC in cirrhosis: **Metanalysis of RCTs**



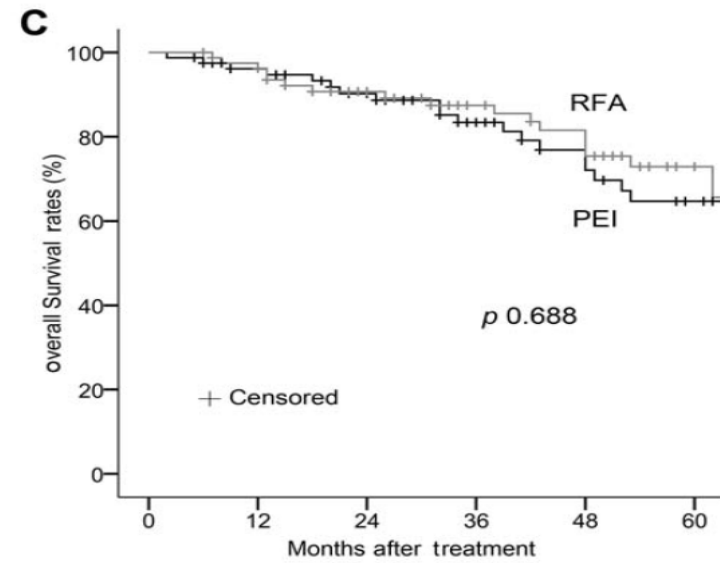
## Single HCC < 2 cm : are percutaneous PEI and RFA equally effective ? Studio multicentrico : Roma , Napoli, Torino , Piacenza , Bologna

- Inclusi nello studio 244 pazienti di cui 108 trattati con PEI e 136 con RFA con un follow-up medio di 27 e 34 mesi .
- I tassi di sopravvivenza a 1, 3 e 5 anni sono stati del 97; 83,3 e 64,6% nel gruppo PEI e 97,7; 77,1 e 62,3% nel gruppo RFA .
- I tassi di recidiva tumorale a 1, 3 e 5 anni sono stati pari al 16,1; 61,4 e 79,4% nel gruppo PEI e 20,4; 47,7 e 57,4% nel gruppo RFA . La recidiva locale non ha condizionato la sopravvivenza globale.
- In conclusione, PEI e RFA hanno dimostrato eguale efficacia nel trattamento dell'HCC < 2 cm . La scelta della tecnica di ablazione migliore deve essere valutata caso per caso tenendo conto della esperienza dell'operatore, sede dell'HCC e bilancio costi-efficacia.



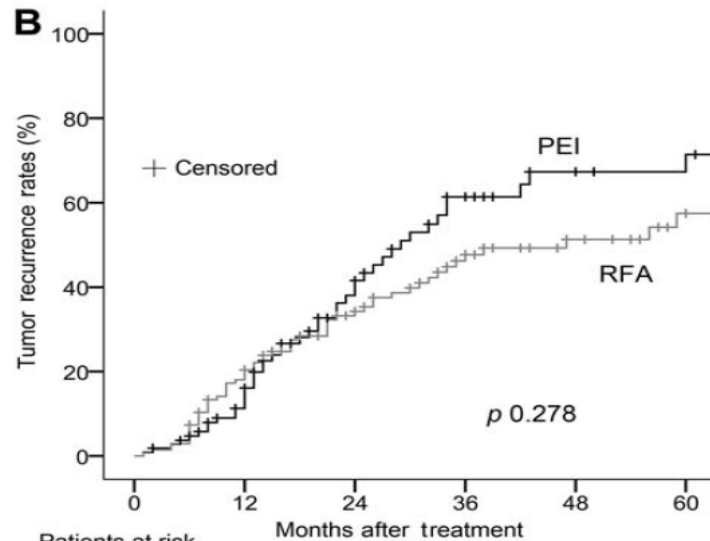
Patients at risk

PEI	108	83	58	42	30	24
RFA	136	124	88	60	43	21



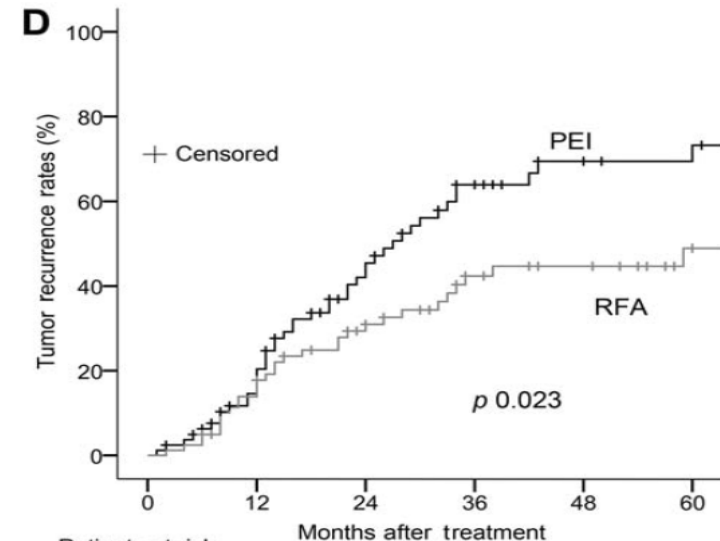
Patients at risk

PEI	81	69	57	42	30	24
RFA	81	71	58	46	37	20



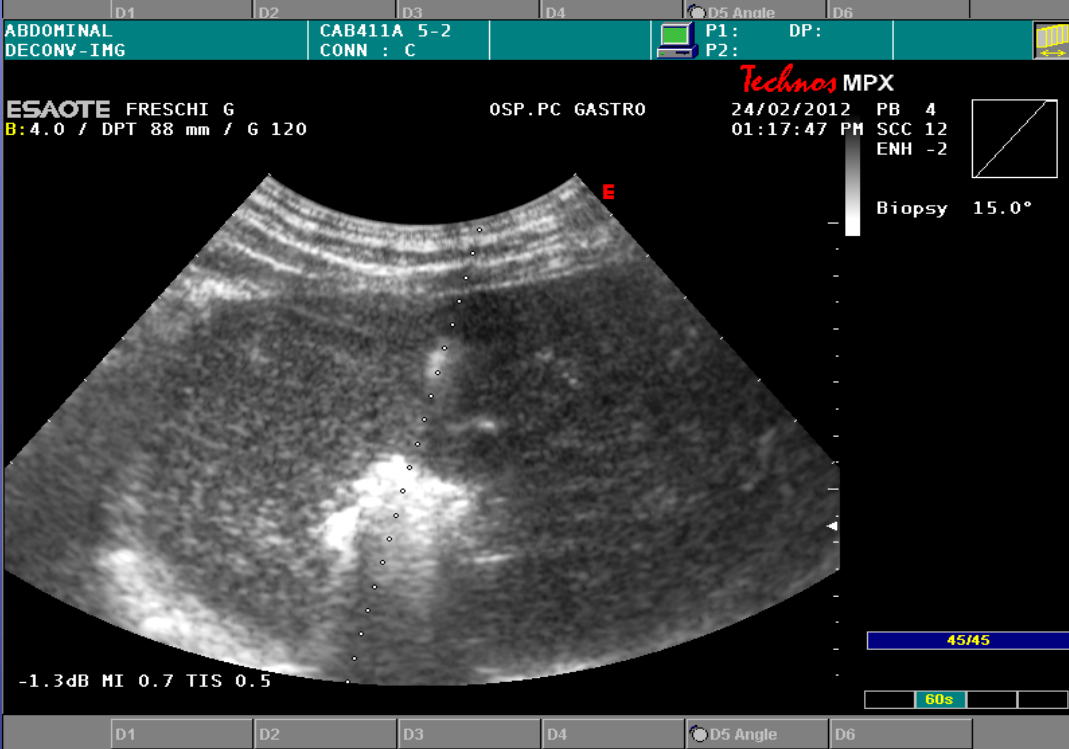
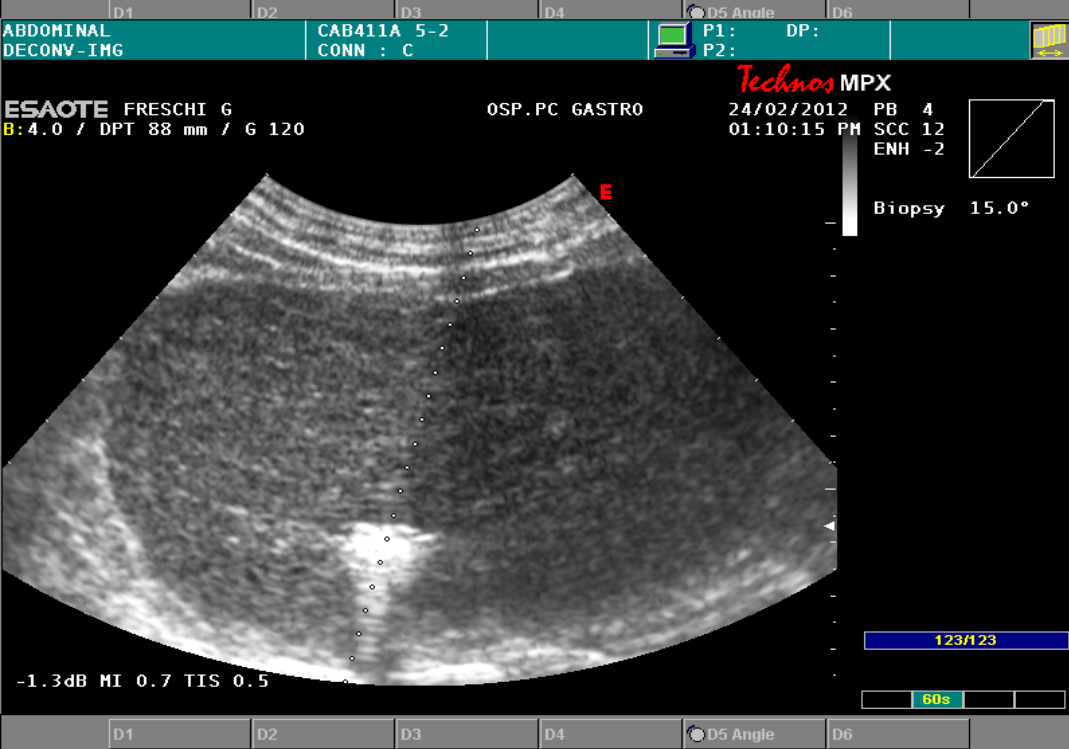
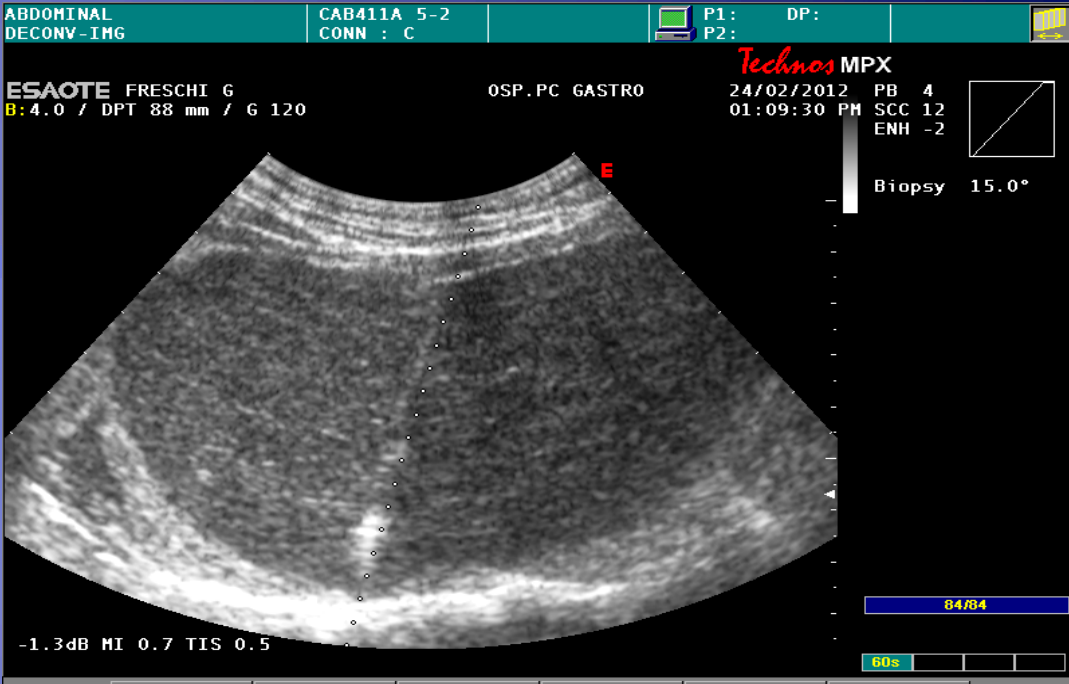
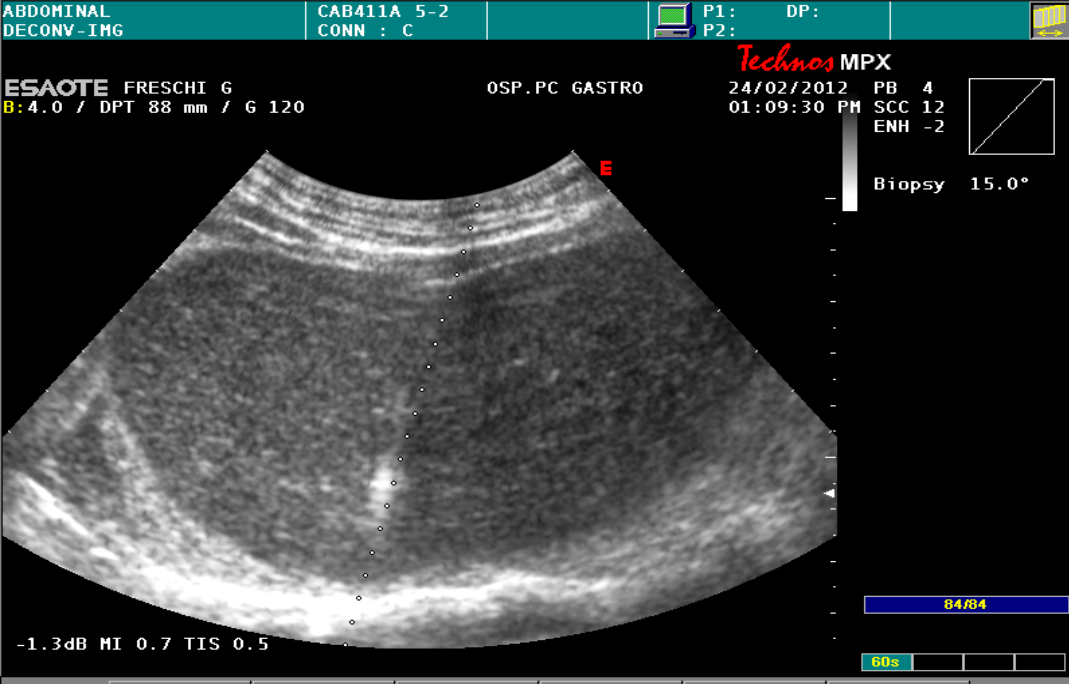
Patients at risk

PEI	108	73	34	16	9	7
RFA	136	104	65	36	23	12

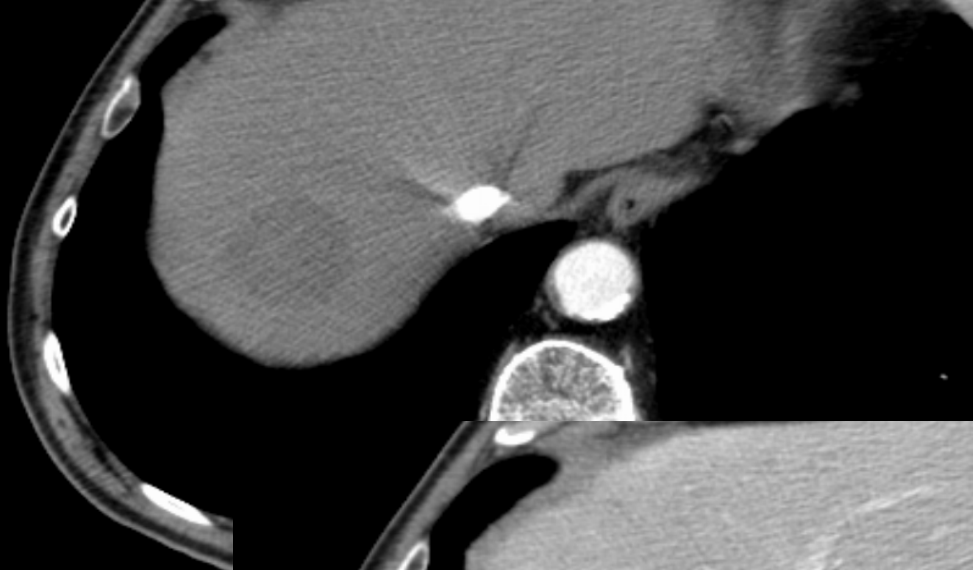


Patients at risk

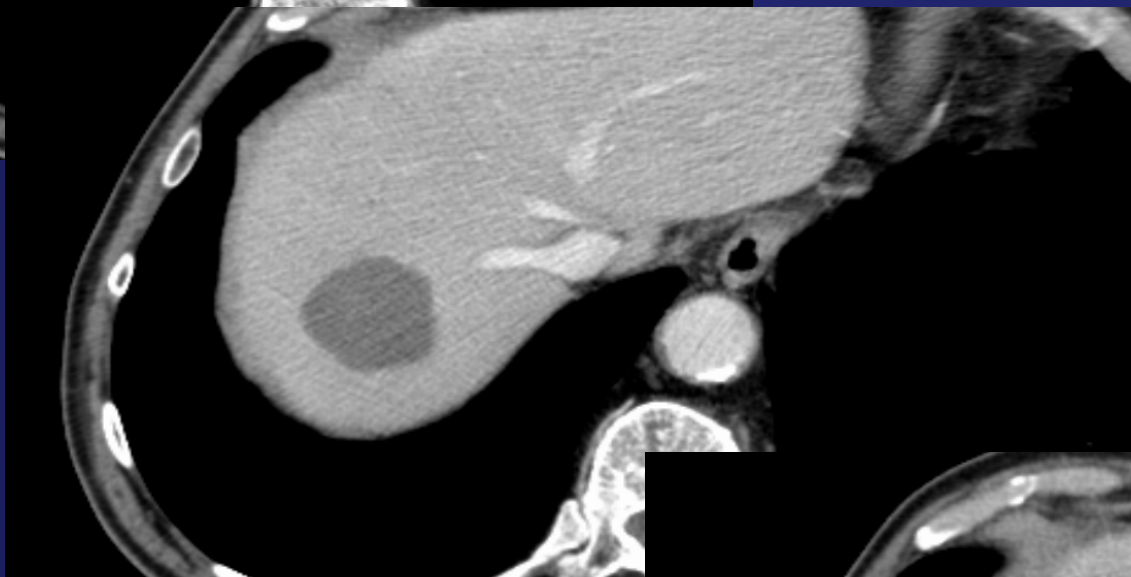
PEI	81	58	33	16	9	7
RFA	81	63	44	26	21	10



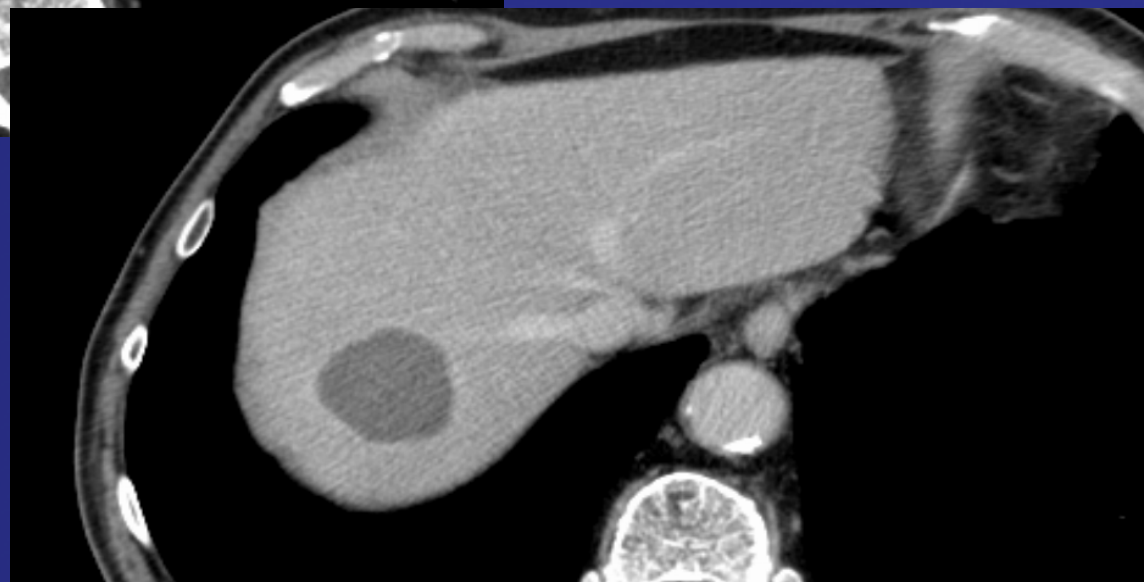




**Fase arteriosa**



**Fase portale**



**Fase tardiva**



ESAOTE FRESCHI G  
B:4.0 / DPT 88 mm / G 120

OSP.PC GASTRO

22/02/2012 PB 4  
01:37:45 PM SCC 12  
ENH -2



Biopsy 15.0°



-1.3dB MI 0.7 TIS 0.5

60s

D1 D2 D3 D4 D5 Angle D6

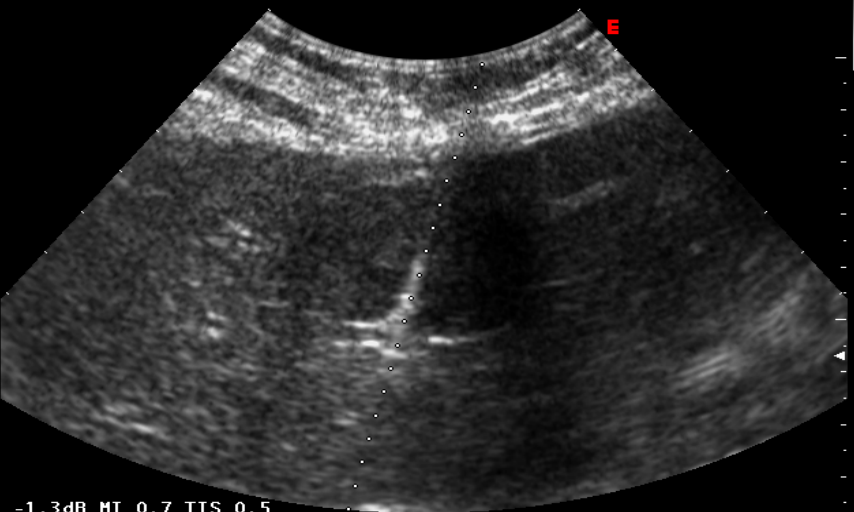
ESAOTE FRESCHI G  
B:4.0 / DPT 88 mm / G 120

OSP.PC GASTRO

22/02/2012 PB 4  
01:37:45 PM SCC 12  
ENH -2



Biopsy 15.0°



-1.3dB MI 0.7 TIS 0.5

60s

D1 D2 D3 D4 D5 Angle D6

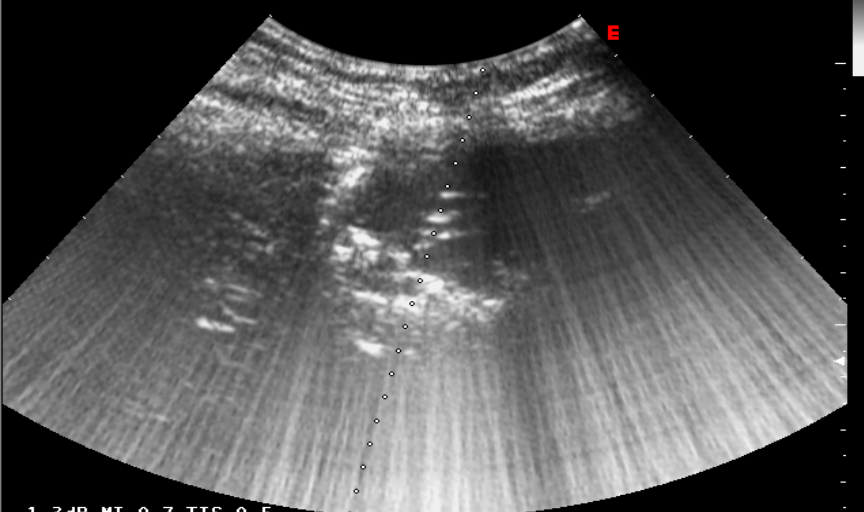
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B:4.0 / DPT 88 mm / G 120

OSP.PC GASTRO

22/02/2012 PB 4  
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ENH -2



Biopsy 15.0°



-1.3dB MI 0.7 TIS 0.5

60s

D1 D2 D3 D4 D5 Angle D6

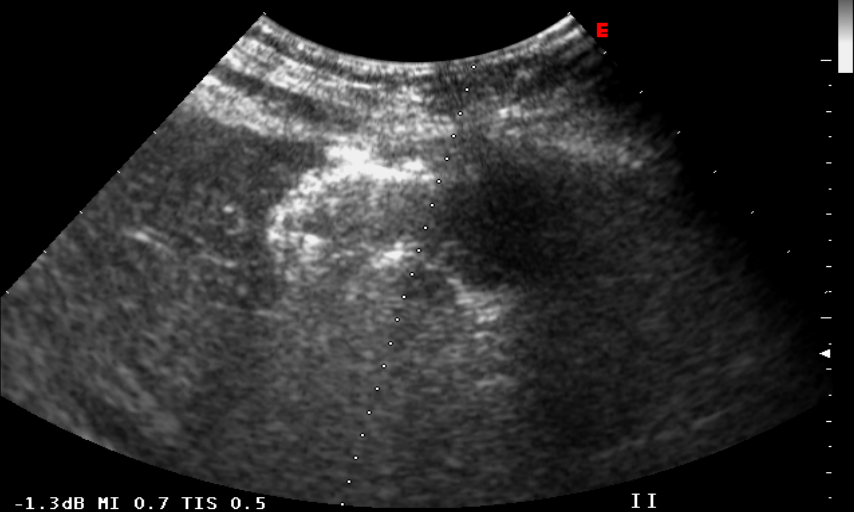
ESAOTE FRESCHI G  
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OSP.PC GASTRO

22/02/2012 PB 4  
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ENH -2



Biopsy 15.0°



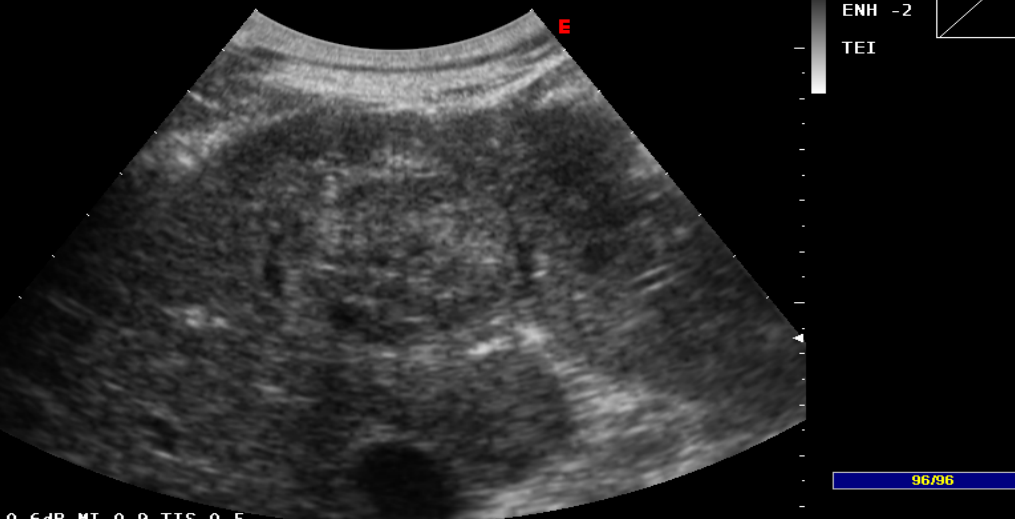
-1.3dB MI 0.7 TIS 0.5

60s

D1 D2 D3 D4 D5 Angle D6

ABDOMINAL DECONV IMAGING CA430E 5-2 P1: DP: P2:

**ESAOE AMBROGGI S** OSP.PC GASTRO **Technos MPX** 09/10/2007 PB 3  
 B:RES / DPT 94 mm / G 115 11:50:08 PM SCC 9  
 ENH -2  
 TEI



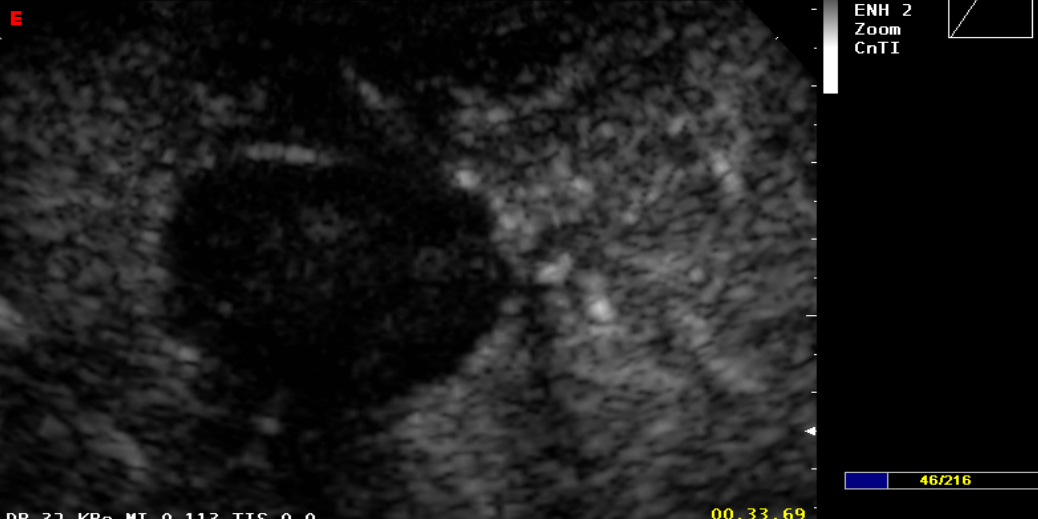
-0.6dB MI 0.9 TIS 0.5 96/96

60s

D1 D2 D3 D4 D5 Angle D6

ABDOMINAL CnTI SonoVue CA430E 5-2 P1: DP: P2:

**ESAOE AMBROGGI S** OSP.PC GASTRO **Technos MPX** 09/10/2007 PB 5  
 B:PEN / DPT 94 mm / G 110 11:54:30 PM SCC 10  
 ENH 2  
 Zoom  
 CnTI



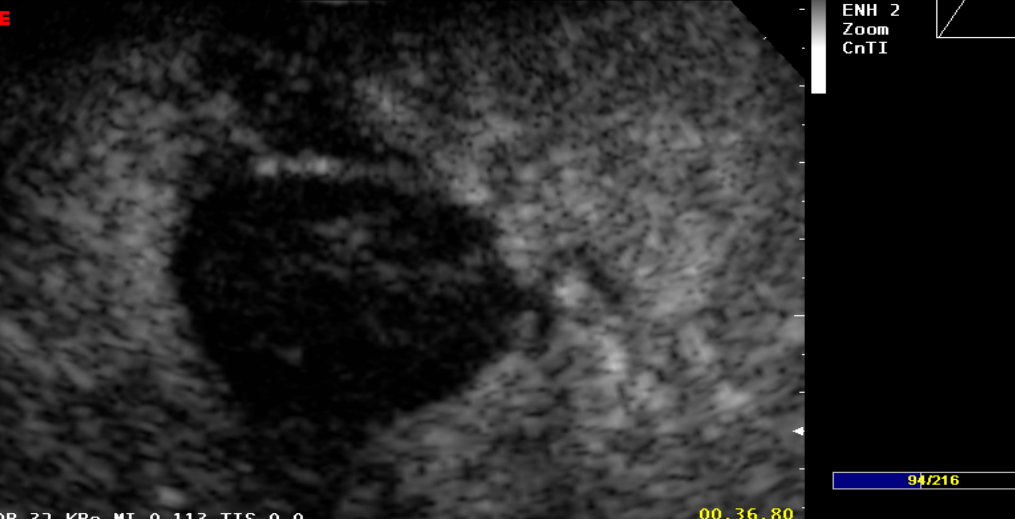
DP 32 KPa MI 0.113 TIS 0.0 46/216

00.33.69  
01.16 60s

D1 C-Capt: Off D2 D3 Chrono Reset D4 Start/Stop D5 Fund D6 Flash

ABDOMINAL CnTI SonoVue CA430E 5-2 P1: DP: P2:

**ESAOE AMBROGGI S** OSP.PC GASTRO **Technos MPX** 09/10/2007 PB 5  
 B:PEN / DPT 94 mm / G 110 11:54:34 PM SCC 10  
 ENH 2  
 Zoom  
 CnTI



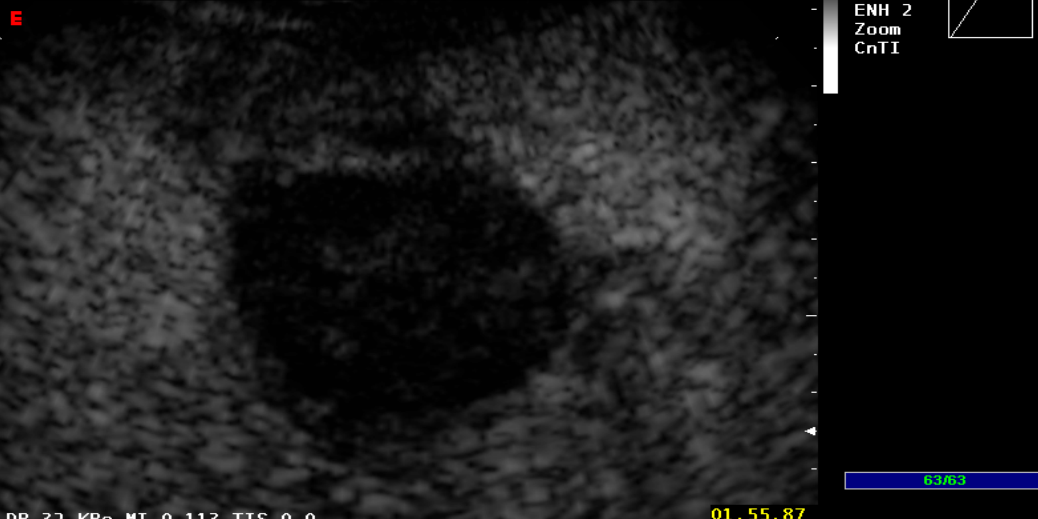
DP 32 KPa MI 0.113 TIS 0.0 94/216

00.36.80  
01.26 60s

D1 C-Capt: Off D2 D3 Chrono Reset D4 Start/Stop D5 Fund D6 Flash

ABDOMINAL CnTI SonoVue CA430E 5-2 P1: DP: P2:

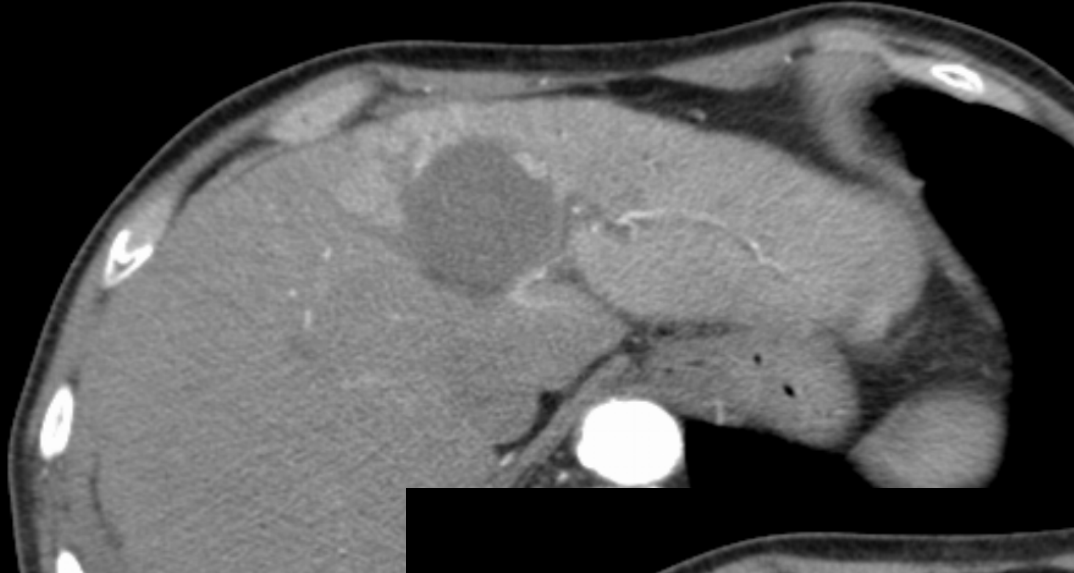
**ESAOE AMBROGGI S** OSP.PC GASTRO **Technos MPX** 09/10/2007 PB 5  
 B:PEN / DPT 94 mm / G 110 11:55:57 PM SCC 10  
 ENH 2  
 Zoom  
 CnTI



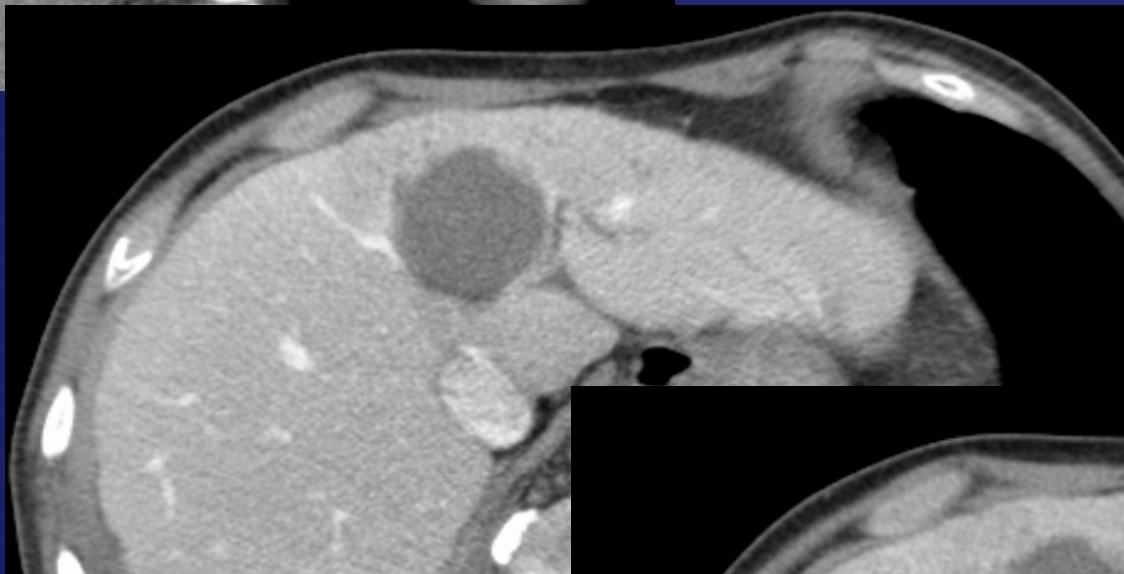
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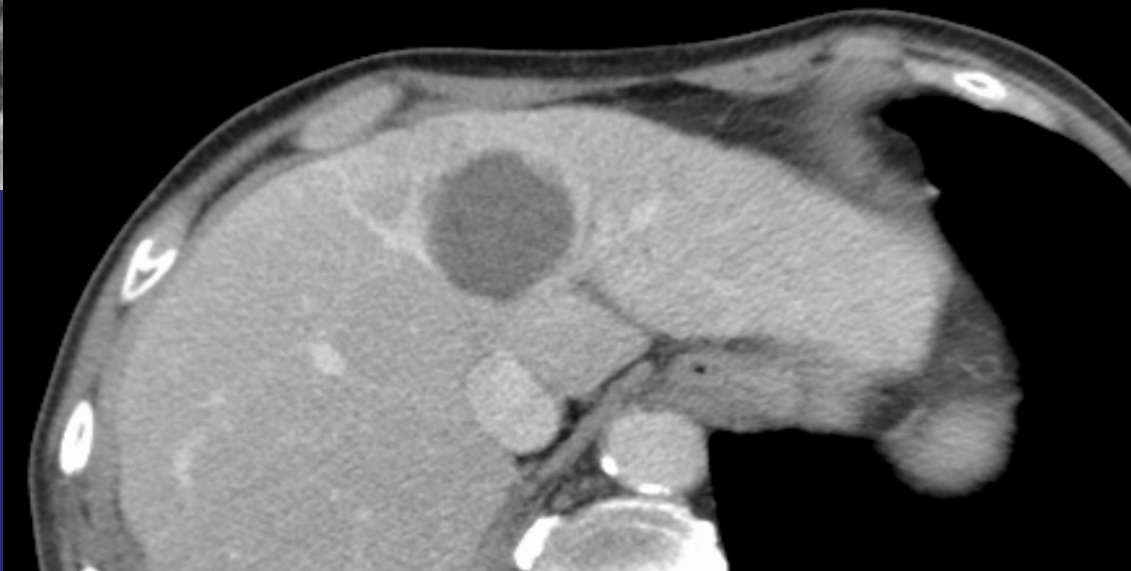
D1 C-Capt: Off D2 D3 Chrono Reset D4 Start/Stop D5 Fund D6 Flash



**Fase arteriosa**

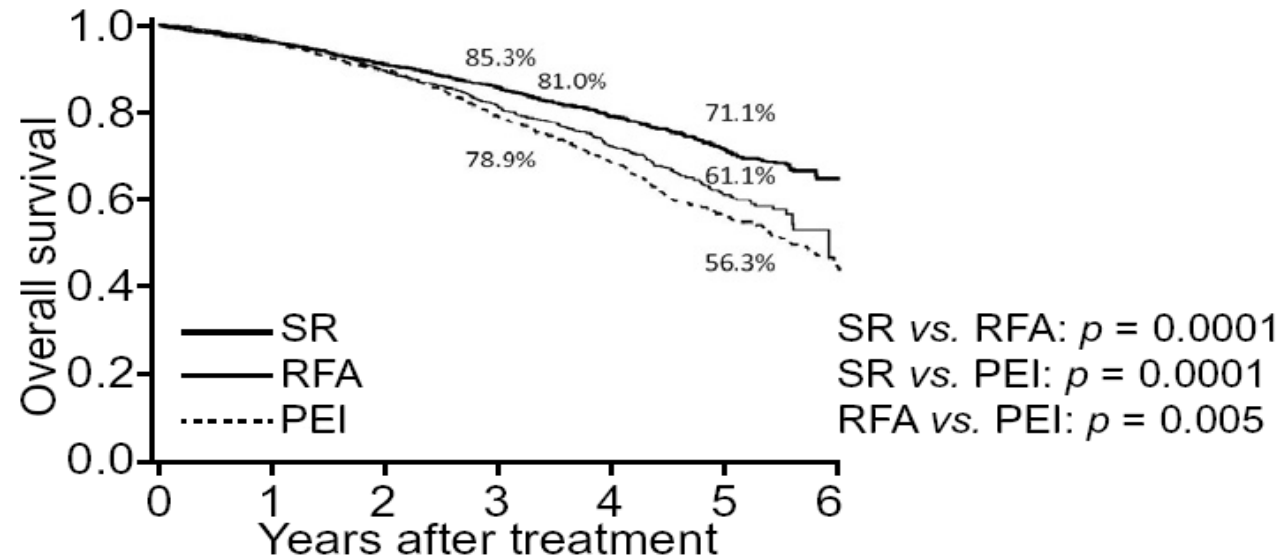


**Fase portale**



**Fase tardiva**

# Sopravvivenza dopo SR, RFA e PEI nello studio di coorte giapponese di 12.968 pazienti con HCC dal 2000 al 2005

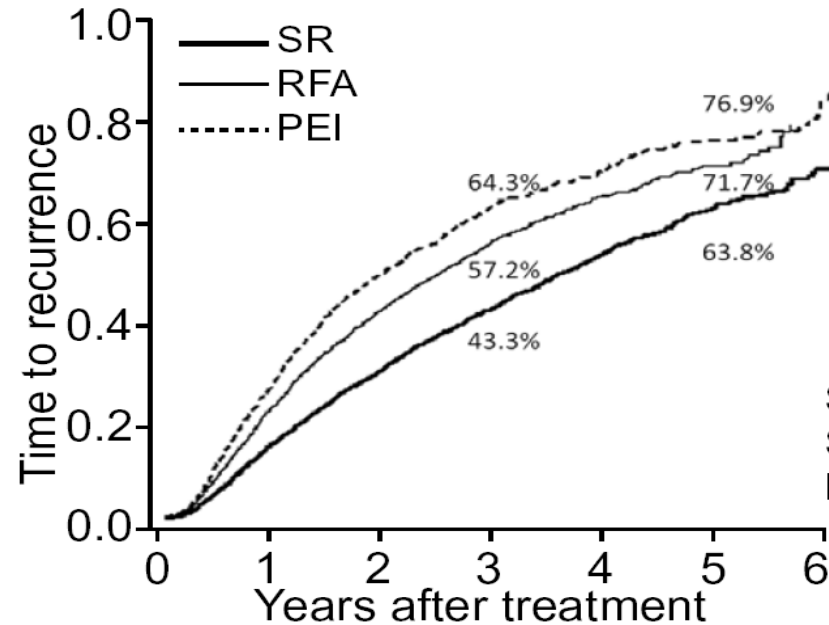


## Patients at risk

SR	5361	3833	2570	1680	894	400	29
RFA	5548	3780	2328	1264	569	160	5
PEI	2059	1595	1112	718	444	247	58

Hasegawa et al J Hepatology 2013

# Curve di recidiva dopo SR, RFA e PEI



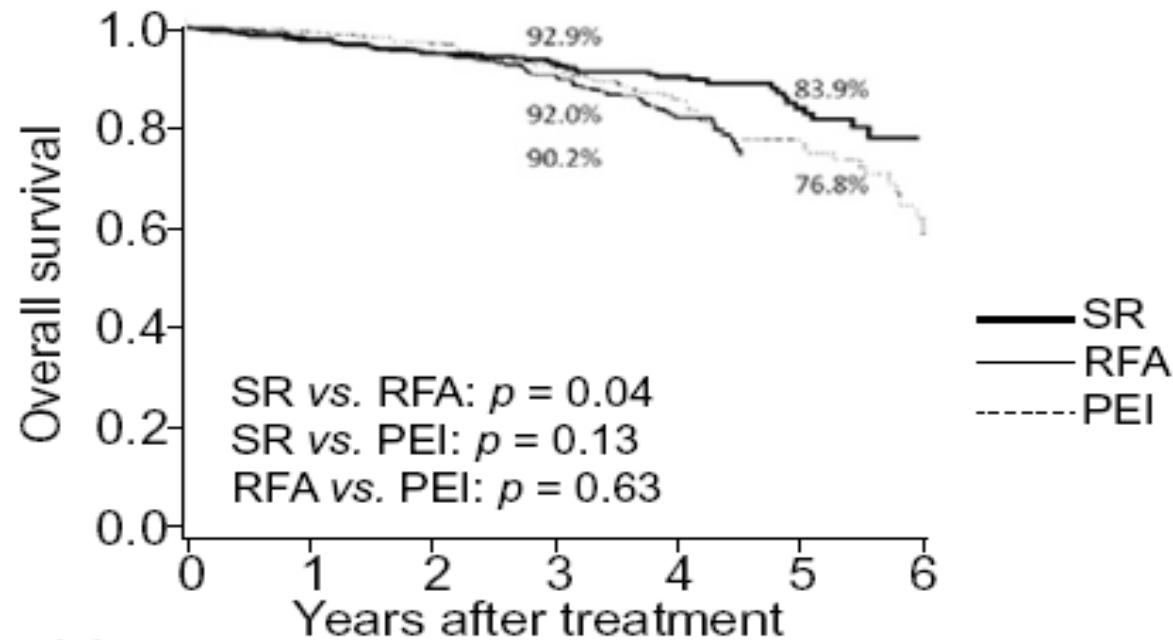
Patients at risk

SR	5361	3265	1844	1039	451	189	15
RFA	5548	2954	1396	591	225	62	4
PEI	2059	1154	583	304	172	90	15

Hasegawa et al J Hepatology 2013



Sopravvivenza dopo SR, RFA e PEI negli HCC in Child A , singolo < 2 cm

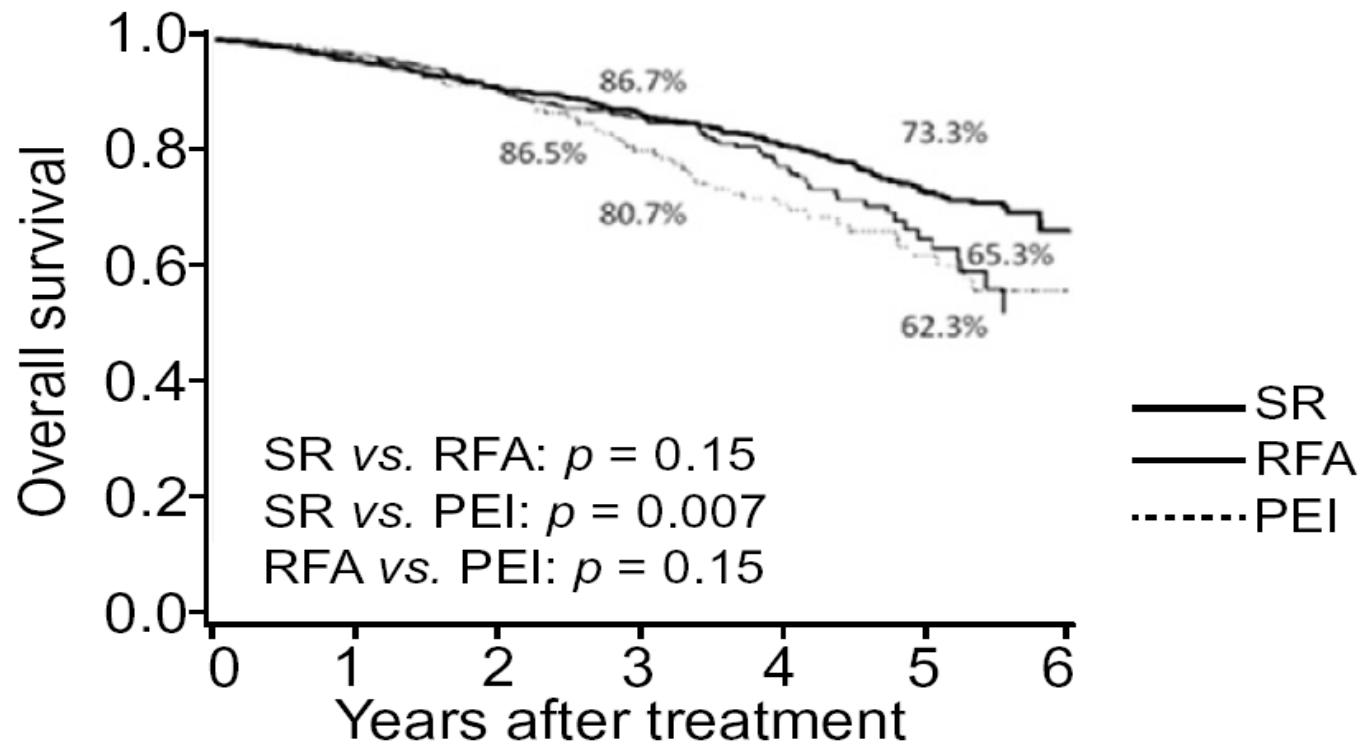


Patients at risk

SR	785	560	392	273	149	75
RFA	1241	834	539	294	136	35
PEI	534	425	308	211	136	82

Hasegawa et al J Hepatology 2013

Sopravvivenza dopo SR, RFA e PEI in HCC Child A , singolo, 2-3 cm



Patients at risk

SR	2565	1879	1215	801	456	194
RFA	1265	869	526	286	123	38
PEI	329	251	172	108	68	40

Hasegawa et al J Hepatology 2013



## Results between RFTA and surgical resection in the management of small HCC : a meta-analysis (six studies : 441 patients in RFA e 436 in RES)

Variables	No. studies furnishing data	Results		OR (95%CI)
		RFA	RES	
Overall survival				
1-year	6 (22,25,30–33)	90.93%	94.95%	0.50 (0.29–0.86)
3-year	5 (22,25,30,31,33)	72.24%	81.09%	0.51 (0.28–0.94)
5-year	5 (22,30–33)	50.54%	60.41%	0.62 (0.45–0.84)
Recurrence-free survival				
1-year	5 (22,25,30–32)	79.02%	83.80%	0.65 (0.44–0.97)
3-year	4 (22,25,30,31)	50.75%	58.95%	0.65 (0.47–0.89)
5-year	4 (22,30–32)	22.30%	33.58%	0.52 (0.35–0.77)
Overall survival in HCCs ≤ 3 cm				
1-year	2 (22,31)	93.83%	99.04%	0.21 (0.04–1.15)
3-year	2 (22,31)	83.95%	93.27%	0.38 (0.16–0.89)
5-year	2 (22,31)	59.88%	69.23%	0.69 (0.41–1.16)
Local recurrence	3 (22,32,33)	17.04%	4.85%	4.08 (2.03–8.20)
Complication	4 (22,25,30–32)	6.58%	28.21%	0.29 (0.08–1.10)



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## Digestive and Liver Disease

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### Oncology

## Long-term effectiveness of Radiofrequency Ablation for solitary small Hepatocellular Carcinoma: A retrospective analysis of 363 patients

Giampiero Francica<sup>a,\*</sup>, Antonio Saviano<sup>b</sup>, Ilario De Sio<sup>c</sup>, Nicoletta De Matthaeis<sup>b</sup>,  
Franco Brunello<sup>d</sup>, Alessandro Cantamessa<sup>d</sup>, Antonio Giorgio<sup>e</sup>, Umberto Scognamiglio<sup>e</sup>,  
Fabio Fornari<sup>f</sup>, Francesco Giangregorio<sup>f</sup>, Fabio Piscaglia<sup>g</sup>, Silvia Gualandi<sup>g</sup>, Eugenio Caturelli<sup>h</sup>,  
Paola Roselli<sup>h</sup>, Gian Ludovico Rapaccini<sup>b</sup>, Maurizio Pompili<sup>b</sup>

<sup>a</sup> Diagnostic and Interventional Unit, "S. Maria della Pietà" Camilliani Hospital, Via San Rocco 9, 80026 Casoria, Italy

<sup>b</sup> Department of Internal Medicine, Catholic University of the Sacred Heart, Rome, Italy

<sup>c</sup> Department of Internal Medicine and Gastroenterology, Second University of Naples, Naples, Italy

<sup>d</sup> Department of Hepatogastroenterology, San Giovanni Battista Hospital, Turin, Italy

<sup>e</sup> IX Infectious Diseases and Interventional Ultrasound Unit, D. Cotugno Hospital, Naples, Italy

<sup>f</sup> Division of Gastroenterology and Hepatology, Piacenza Hospital, Piacenza, Italy

<sup>g</sup> Division of Internal Medicine, Department of Digestive Disease and Internal Medicine, S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy

<sup>h</sup> Gastroenterology Unit, Ospedale Belcolle, Viterbo, Italy

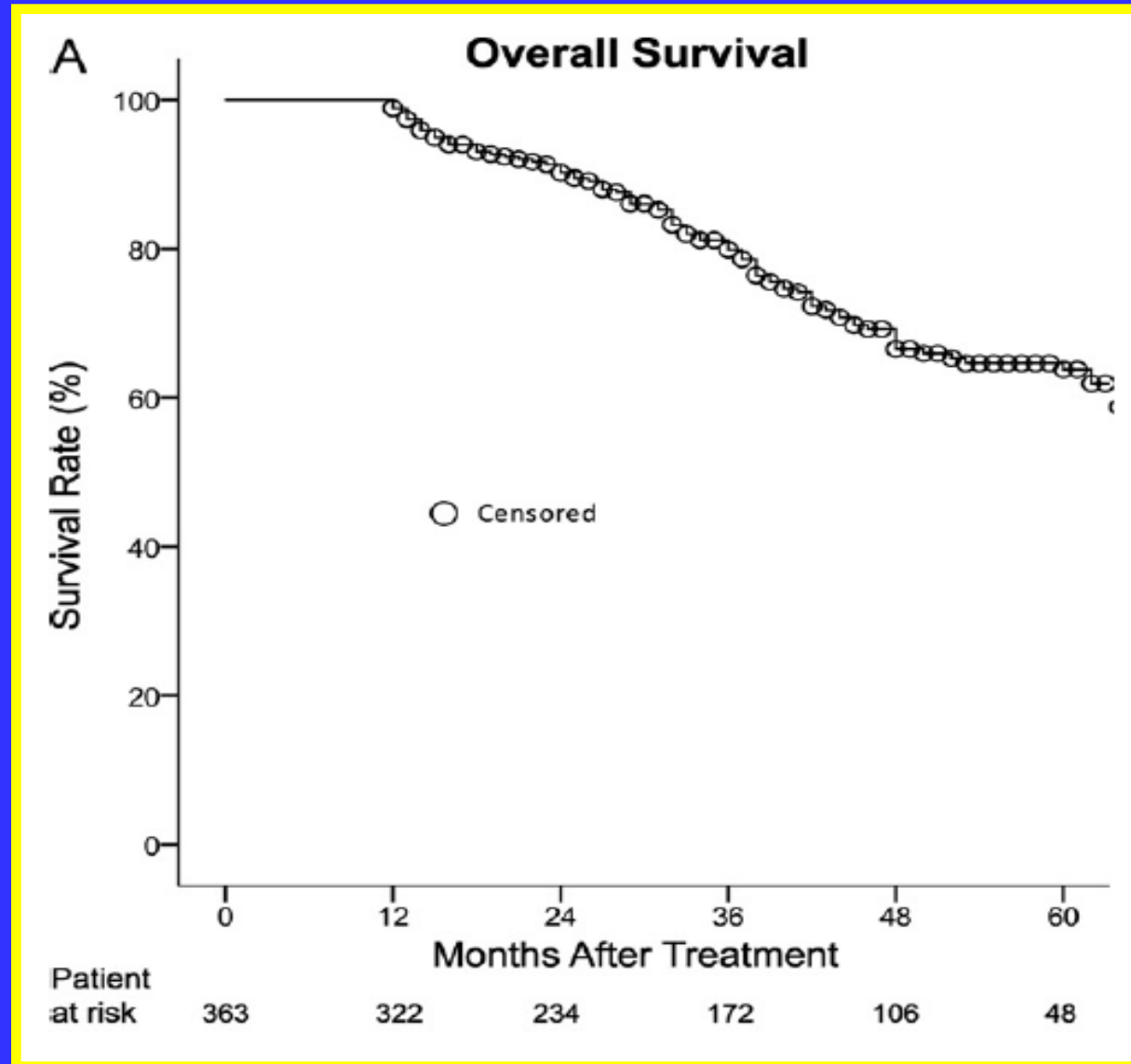
## Long -term effectiveness of RFA for solitary small HCC: A retrospective analysis of 363 patients

Multicentre retrospective analysis of 363 patients with single HCC in very early and early stage ( 127 <2 cm) observed in 7 Italian Centers treated with RFA and a median follow-up period of 37 months

Major complications were observed in 2.2%. The 3- and 5-year OS rates were 80% and 64% . At multivariate analysis only age, ascites and Child-Pugh class > B8 were confirmed as independent predictors of OS .

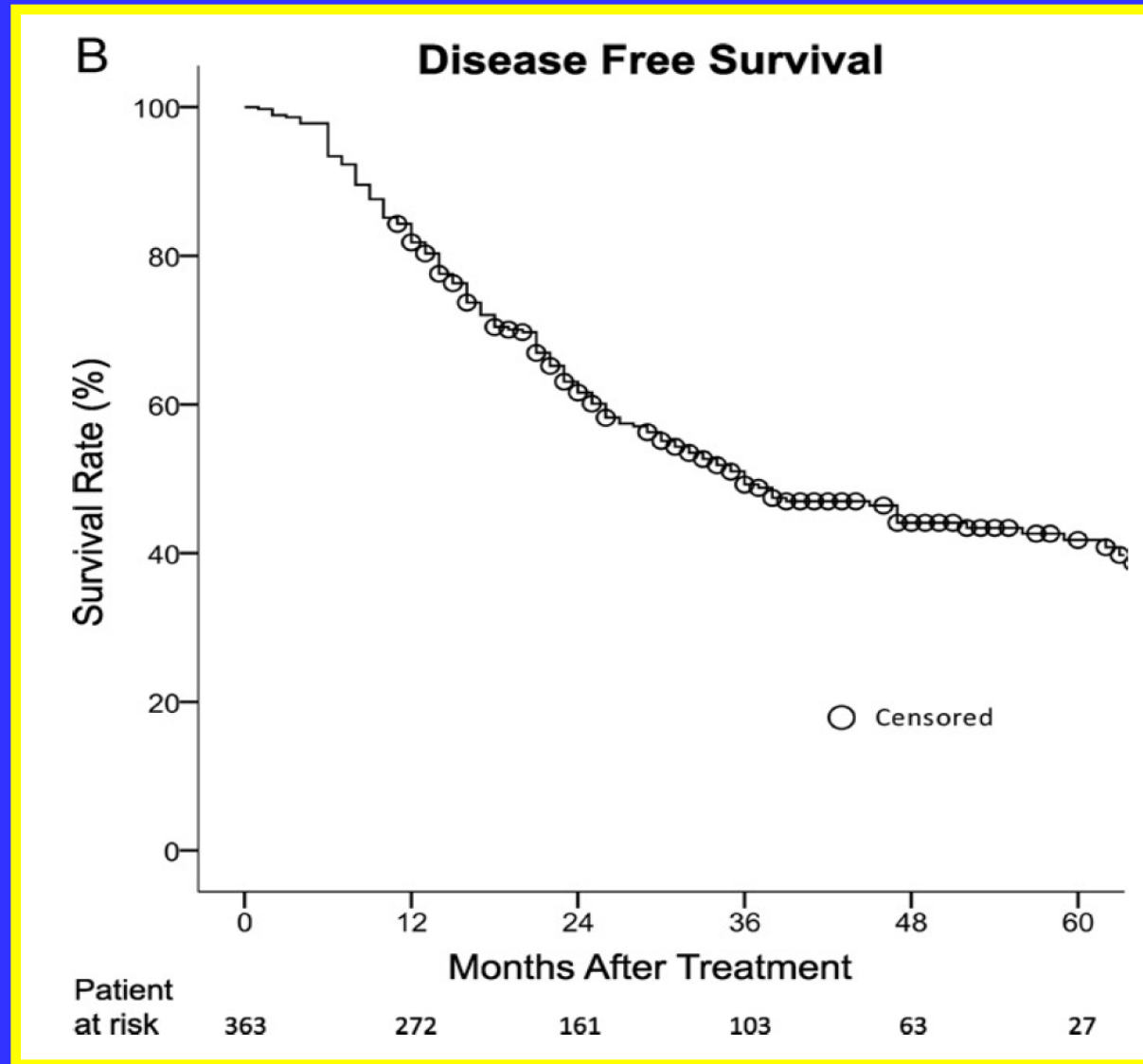
The DFS was 36 months (50% and 41.8% at 3-and 5-year) without significant difference between HCC < 2 cm and between 2 and 3 cm .

# Long-term effectiveness of RFTA for solitary small HCC

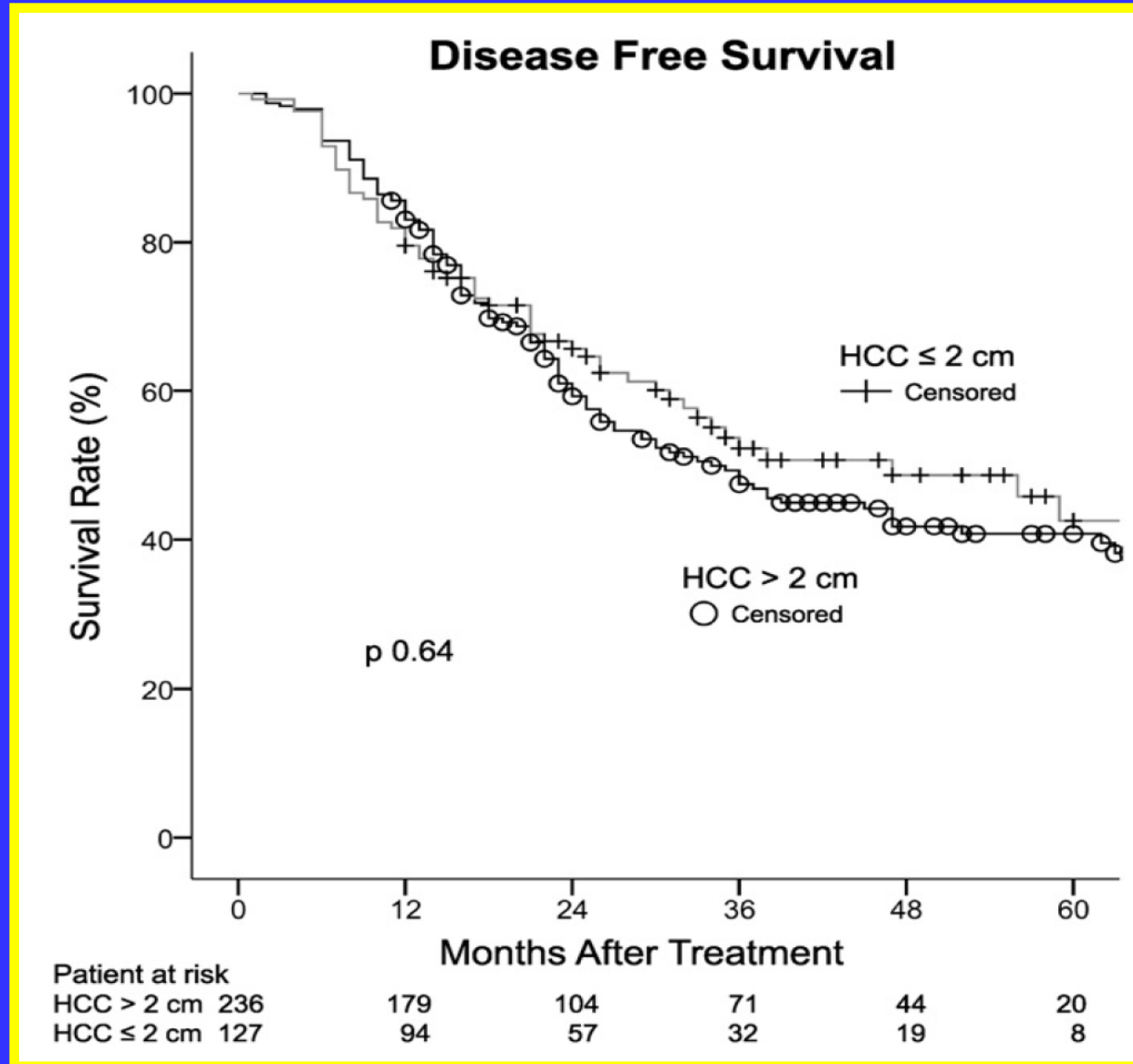


Francica et al Dig Liv Dis 2013

# Long-term effectiveness of RFTA for solitary small HCC

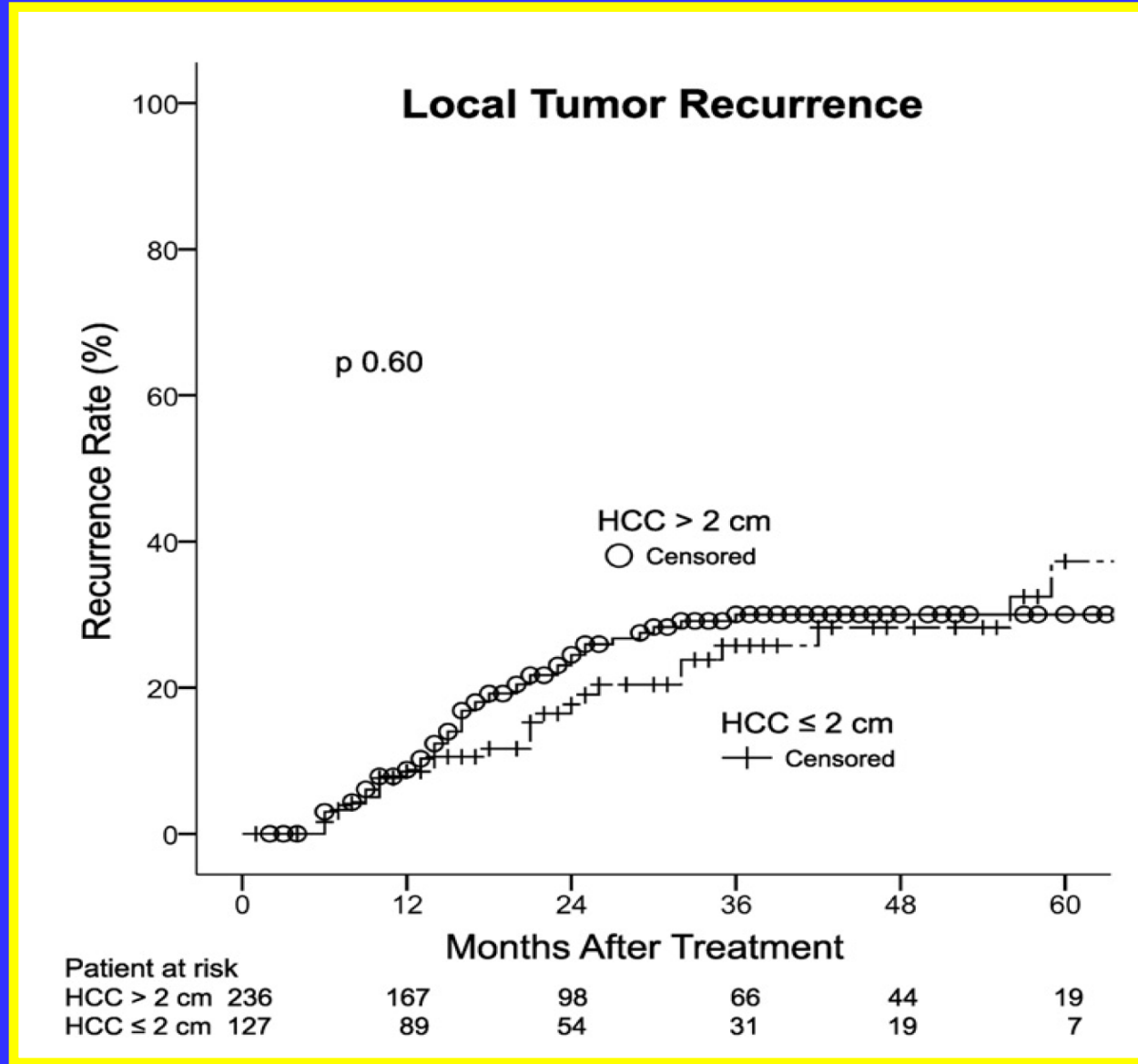


# Long-term effectiveness of RFTA for solitary small HCC



Francica et al Dig Liv Dis 2013

# Long-term effectiveness of RFTA for solitary small HCC



Francica et al Dig Liv Dis 2013



## **Long-term effectiveness of resection and radiofrequency ablation for single hepatocellular carcinoma $\leq 3$ cm. Results of a multicenter Italian survey**

Maurizio Pompili<sup>1,\*</sup>, Antonio Saviano<sup>1</sup>, Nicoletta de Matthaeis<sup>1</sup>, Alessandro Cucchetti<sup>2</sup>, Francesco Ardito<sup>3</sup>, Bruno Federico<sup>4</sup>, Franco Brunello<sup>5</sup>, Antonio D. Pinna<sup>2</sup>, Antonio Giorgio<sup>6</sup>, Stefano M. Giulini<sup>7</sup>, Ilario De Sio<sup>8</sup>, Guido Torzilli<sup>9</sup>, Fabio Fornari<sup>10</sup>, Lorenzo Capussotti<sup>11</sup>, Alfredo Guglielmi<sup>12</sup>, Fabio Piscaglia<sup>13</sup>, Luca Aldrighetti<sup>14</sup>, Eugenio Caturelli<sup>15</sup>, Fulvio Calise<sup>16</sup>, Gennaro Nuzzo<sup>3</sup>, Gian Ludovico Rapaccini<sup>1</sup>, Felice Giuliani<sup>3</sup>

<sup>1</sup>Department of Internal Medicine, Università Cattolica del Sacro Cuore, Rome, Italy; <sup>2</sup>Liver and Multiorgan Transplant Unit – Department of General Surgery, S. Orsola Malpighi Hospital, Bologna, Italy; <sup>3</sup>Department of Surgical Sciences, Università Cattolica del Sacro Cuore, Rome, Italy; <sup>4</sup>Department of Health and Sport Sciences, University of Cassino, Italy; <sup>5</sup>Department of Hepatology and Gastroenterology, San Giovanni Battista Hospital, Turin, Italy; <sup>6</sup>IX Infectious Disease and Interventional Ultrasound Unit, D Cotugno Hospital, Naples, Italy; <sup>7</sup>Department of Surgery, Spedali Civili University Hospital, Brescia University, Brescia, Italy; <sup>8</sup>Internal Medicine and Gastroenterology, University of Naples, Naples, Italy; <sup>9</sup>III Department of General Surgery, Istituto Clinico Humanitas, Milan University, Milan, Italy; <sup>10</sup>Gastroenterology, G. da Saliceto Hospital, Piacenza, Italy; <sup>11</sup>Department of Hepatopancreatobiliary and Digestive Surgery, Ospedale Mauriziano Umberto I, Turin, Italy; <sup>12</sup>Department of Surgery, Gian Battista Rossi University Hospital, Verona University, Verona, Italy; <sup>13</sup>Internal Medicine, S. Orsola Malpighi Hospital, Bologna, Italy; <sup>14</sup>Department of Surgery, Scientific Institute Vita-Salute, San Raffaele University, Milan, Italy; <sup>15</sup>Gastroenterology, Belcolle Hospital, Viterbo, Italy; <sup>16</sup>Unit of Hepatobiliary Surgery and Liver Transplantation, Antonio Cardarelli Hospital, Naples, Italy

# Liver resection and RFA in the treatment of single small (< 3 cm ) HCC : long term effectiveness in a multicenter series.

Studio multicentrico retrospettivo che ha coinvolto 15 UO italiane .

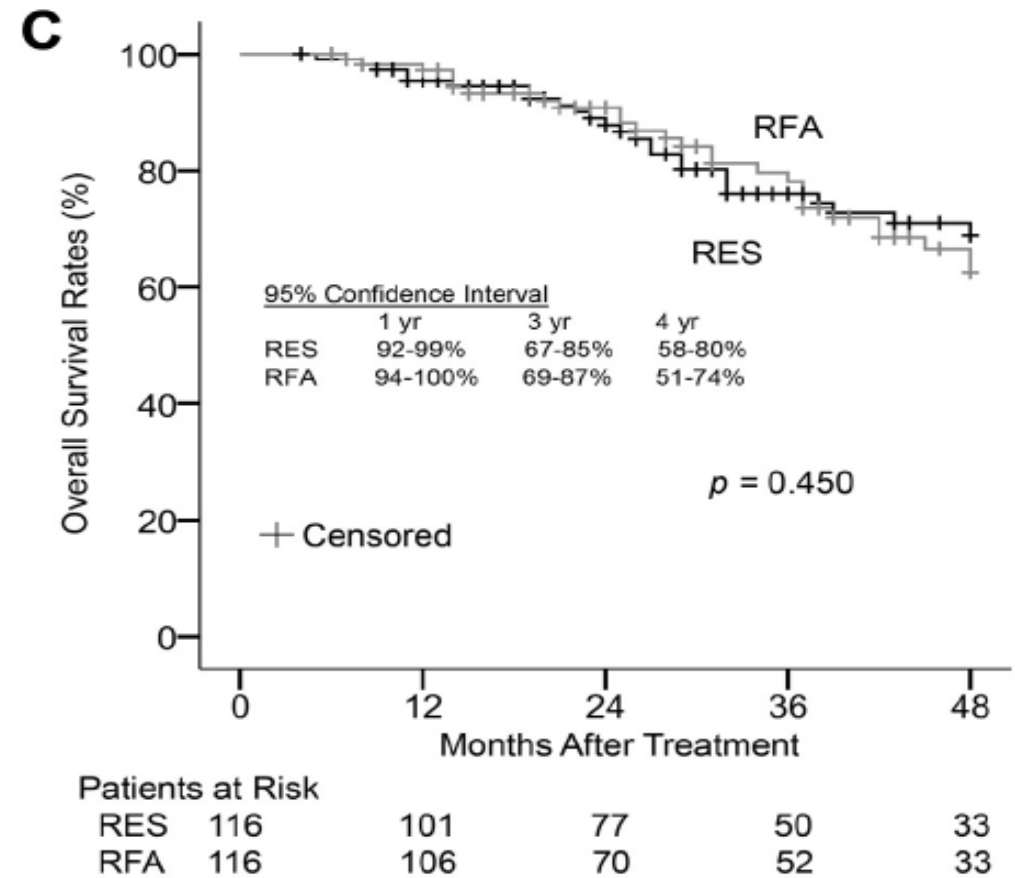
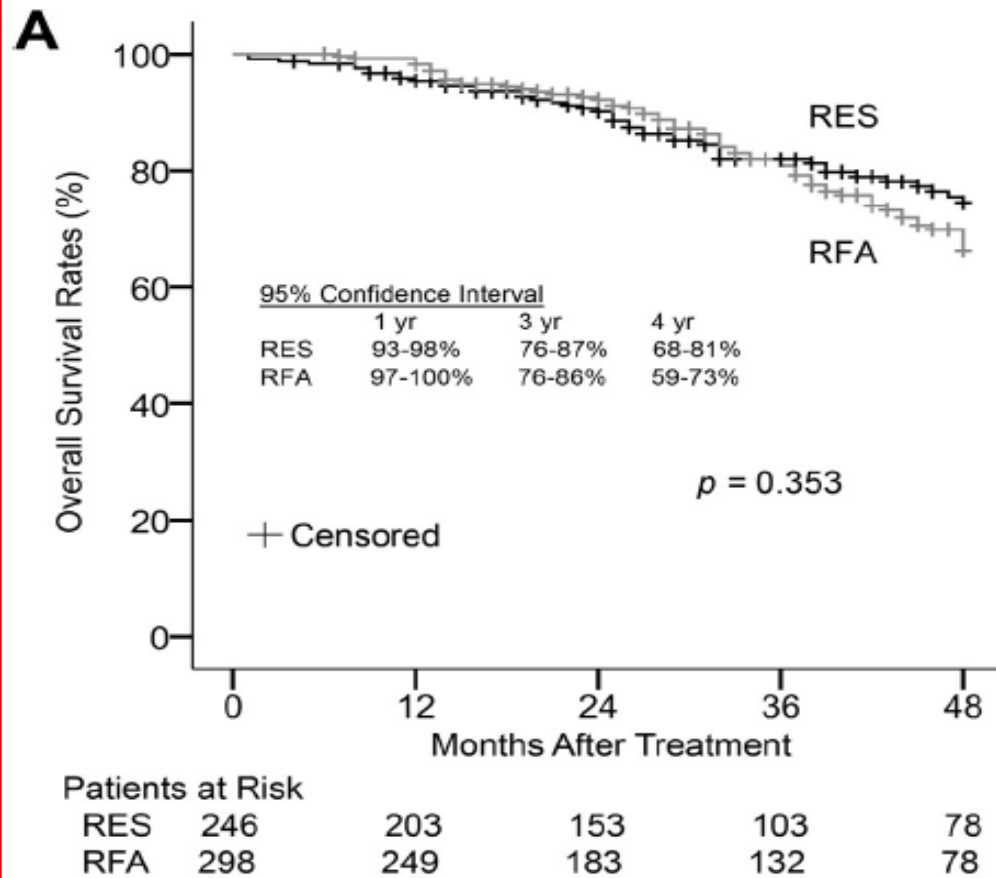
Inclusi nella casistica 246 pazienti sottoposti a resezione chirurgica (RES) e 269 pazienti sottoposti a RFA

Dati Clinici ( RES vs RFA ) : età media: 66 vs 68 ; maschi 81%vs 58%; HCV 65% vs 83%) ; Ipertensione portale 25% vs 52%; Bilirubina 0,89 vs 1,11; Albumina 4,1 vs 3,7; AFP 130 vs 98 ;

Epatocarcinoma di diametro < 2 cm era presente nel 40% vs 36%

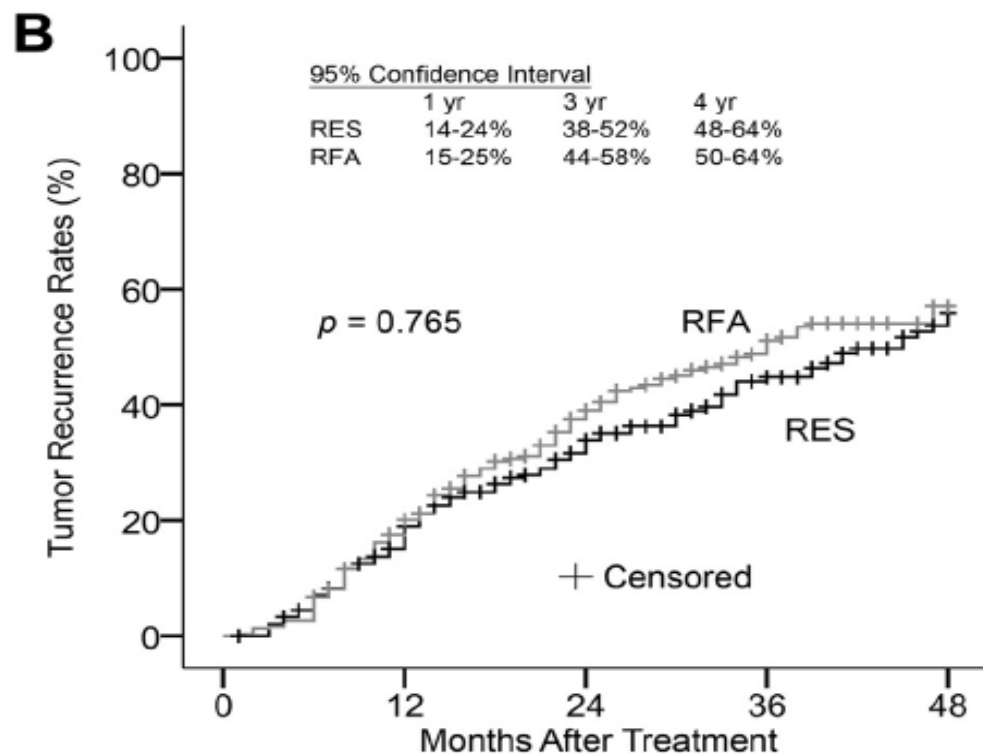
Mortalità perioperatoria :0,8% vs 0 ; complicanze maggiori 4,5% vs 2,2% .

# Curve di sopravvivenza per HCC singolo < 3 cm sottoposto a resezione (RES) e RFA ( assenza di differenze significative)

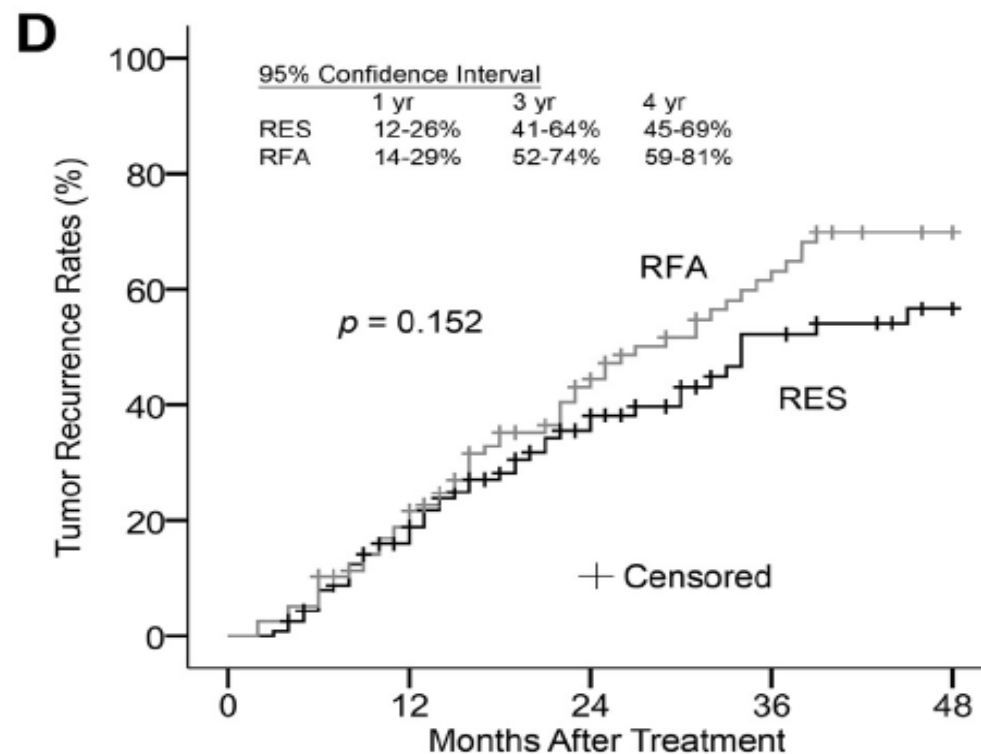


Pompili et al J Hepatology 2013

# Percentuali di recidiva per HCC singolo < 3 cm sottoposto a RES e RFA



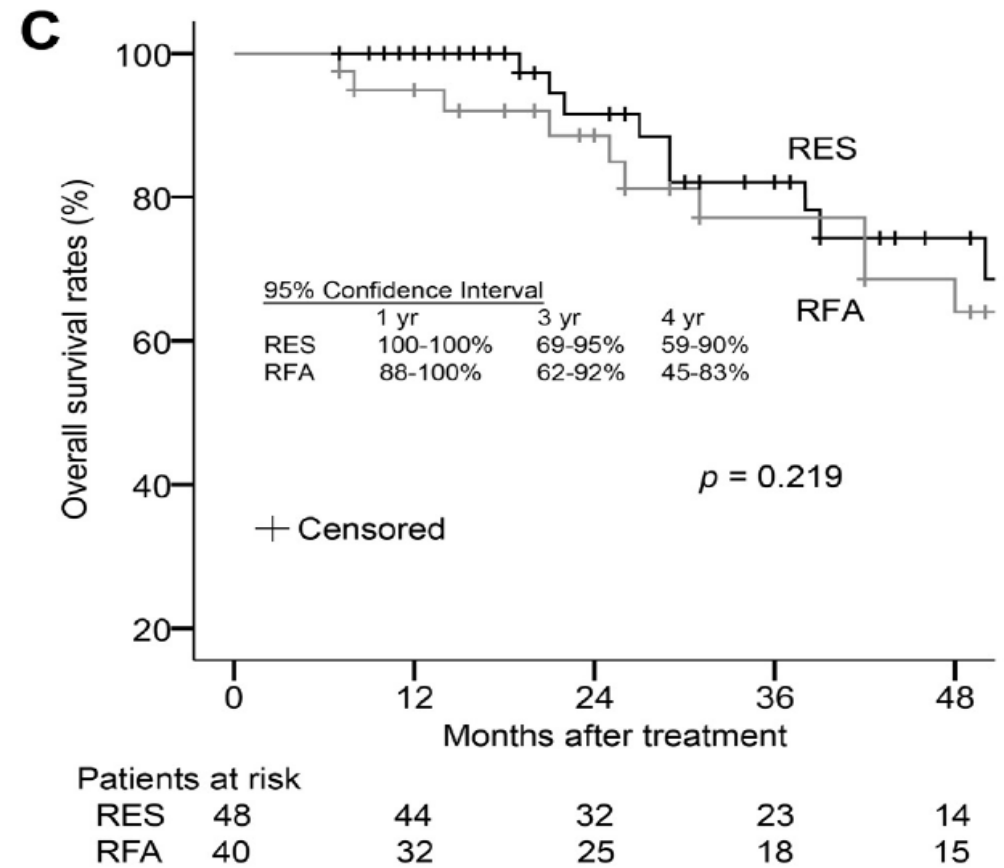
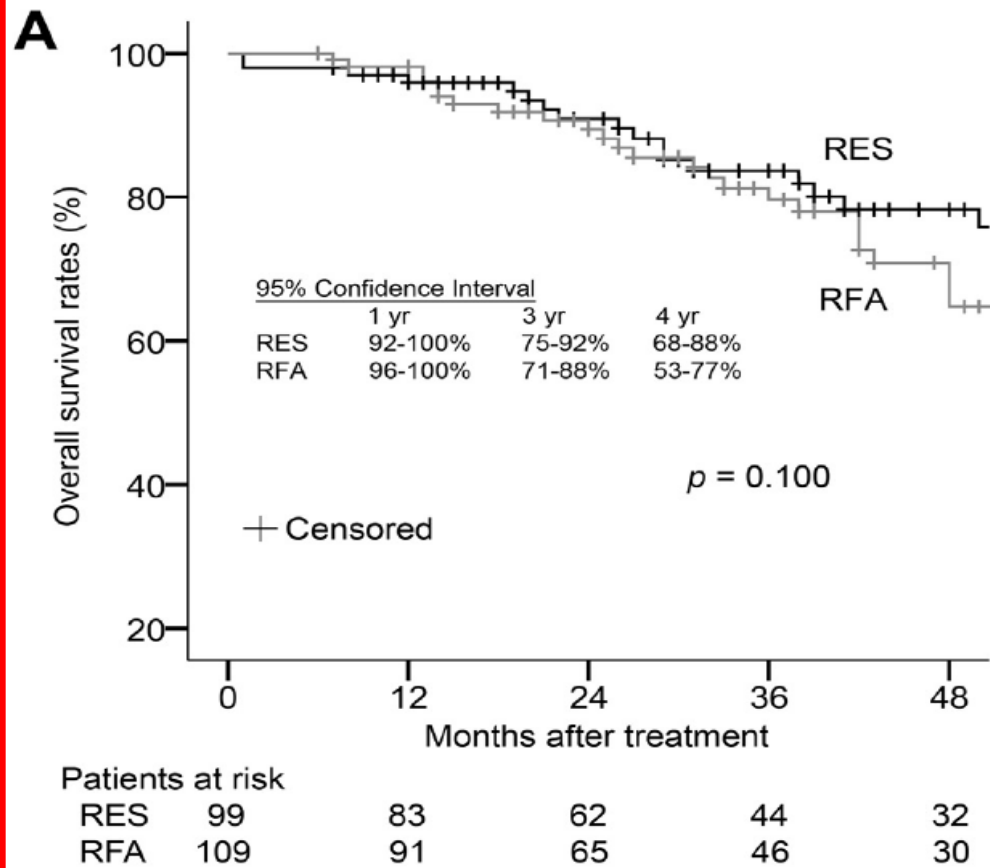
Patients at Risk		0	12	24	36	48
RES	246	175	106	65	39	
RFA	298	205	121	79	46	



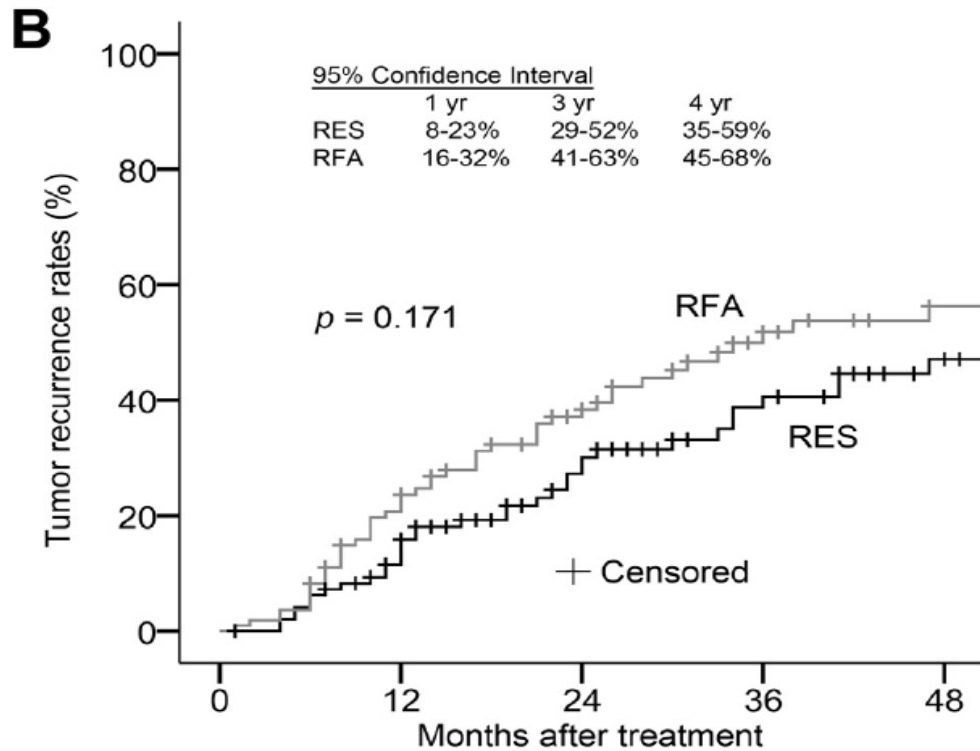
Patients at Risk		0	12	24	36	48
RES	116	87	49	26	16	
RFA	116	86	42	23	12	

Pompili et al J Hepatology 2013

# Percentuali di sopravvivenza per HCC singolo < 2 cm sottoposto a RES e RFA

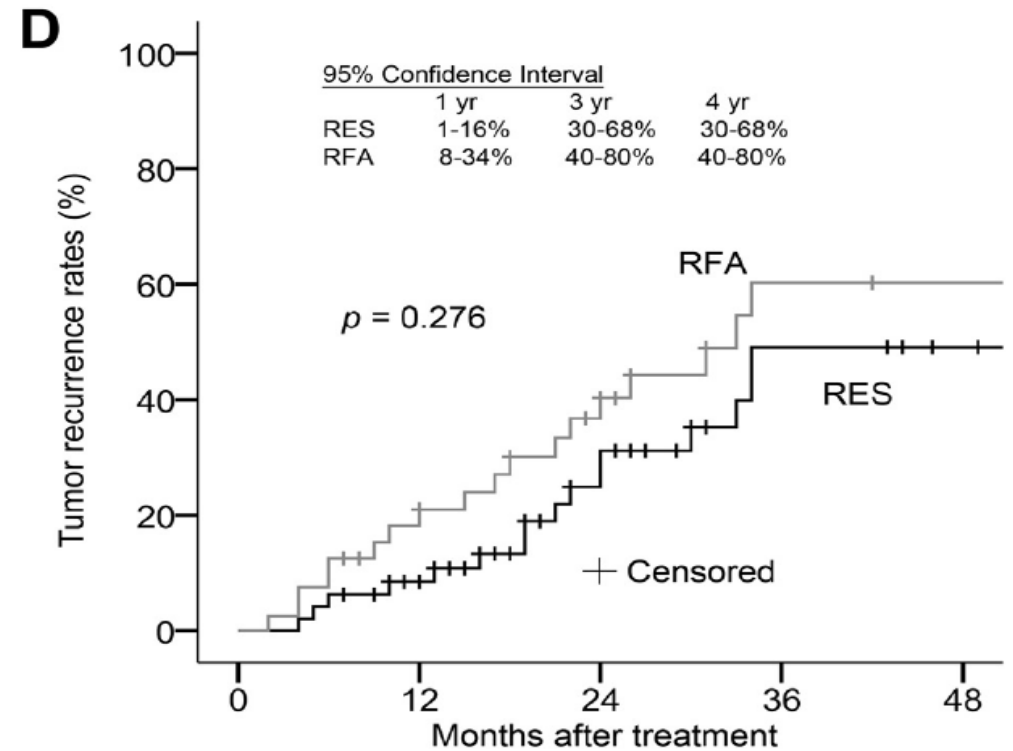


# Percentuali di recidiva per HCC singolo < 2 cm sottoposto a RES e RFA



Patients at risk

	0	12	24	36	48
RES	99	73	46	29	20
RFA	109	73	43	24	15



Patients at risk

	0	12	24	36	48
RES	48	40	24	11	8
RFA	40	29	18	7	6

# Trial multicentrico randomizzato di confronto fra crioablazione e RFTA nel trattamento dell' HCC ( 1-2 lesioni fino a 4 cm )

	<b>Cryoablation (n = 180)</b>	<b>RFA (n = 180)</b>	<b>P Value</b>
Local recurrence	10 (5.6%)	18 (10%)	NS
New recurrence	56 (31.1%)	54 (30%)	NS
Overall survival			NS
1-year	97%	97%	
3-year	67%	66%	
5-year	40%	38%	
Tumor-free survival			NS
1-year	89%	84%	
3-year	54%	50%	
5-year	35%	34%	

RFA, radiofrequency ablation; NS, not significant.



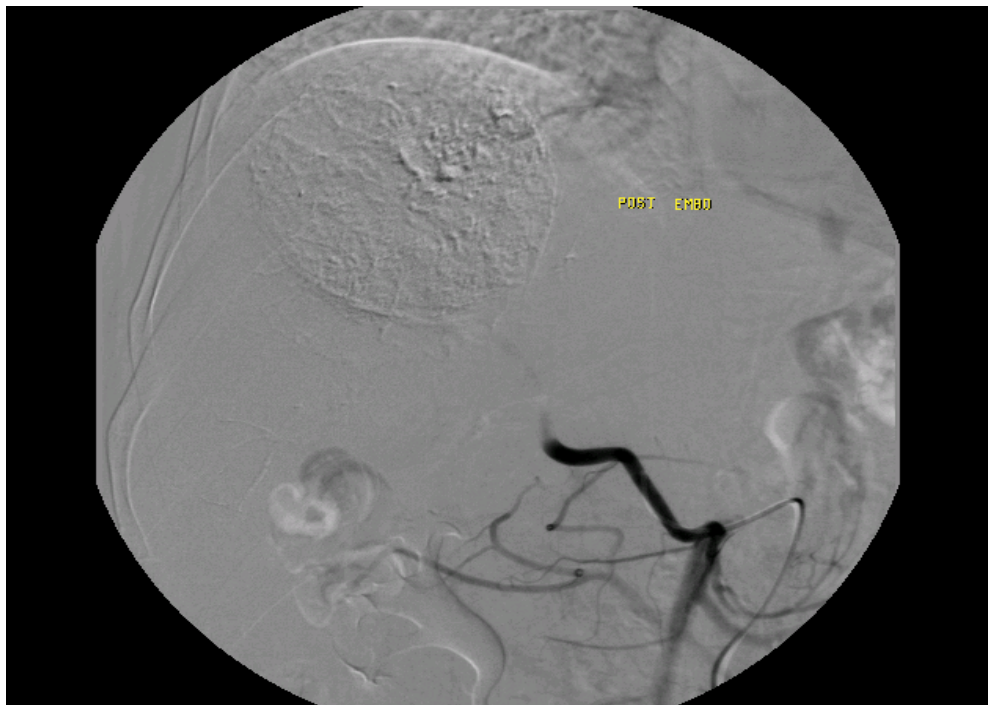
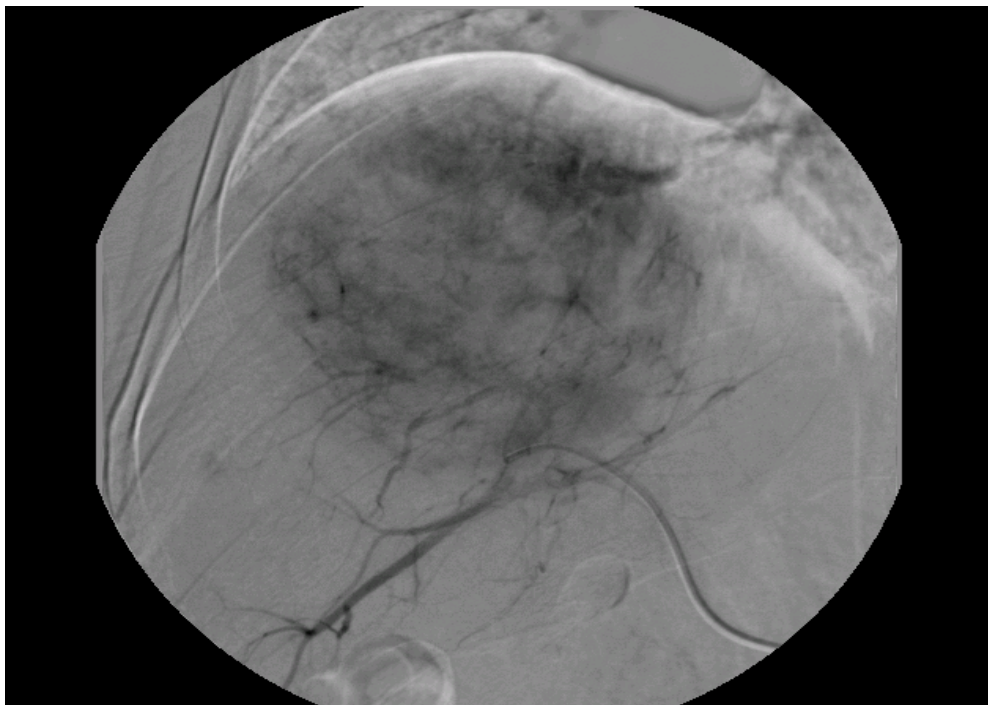
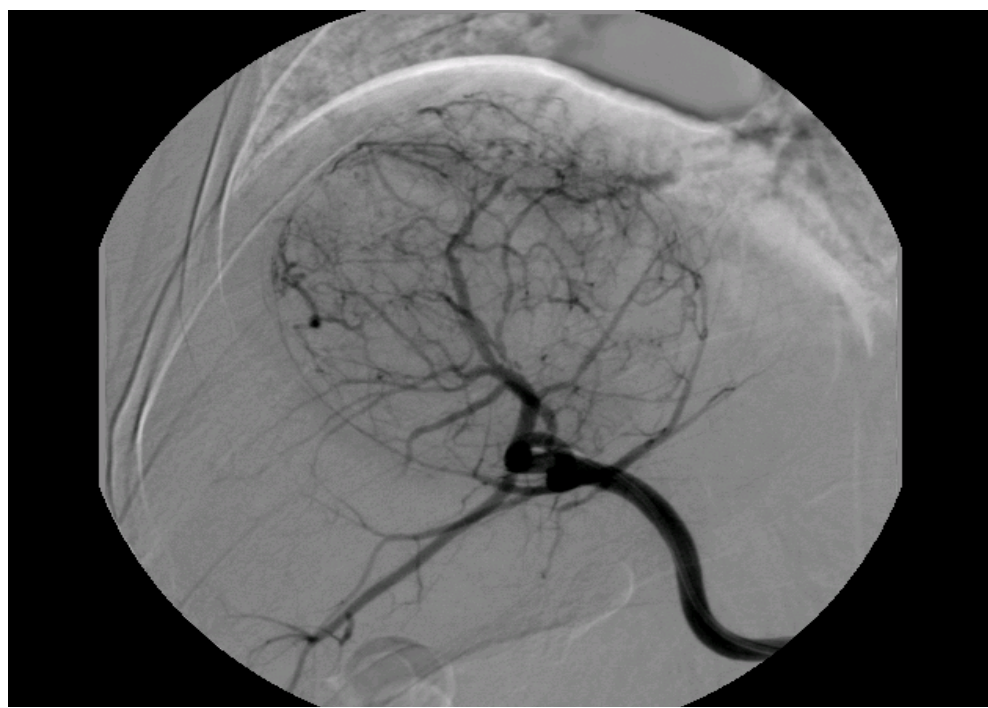
## **EASL–EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma**

European Association for the Study of the Liver\*,  
European Organisation for Research and Treatment of Cancer

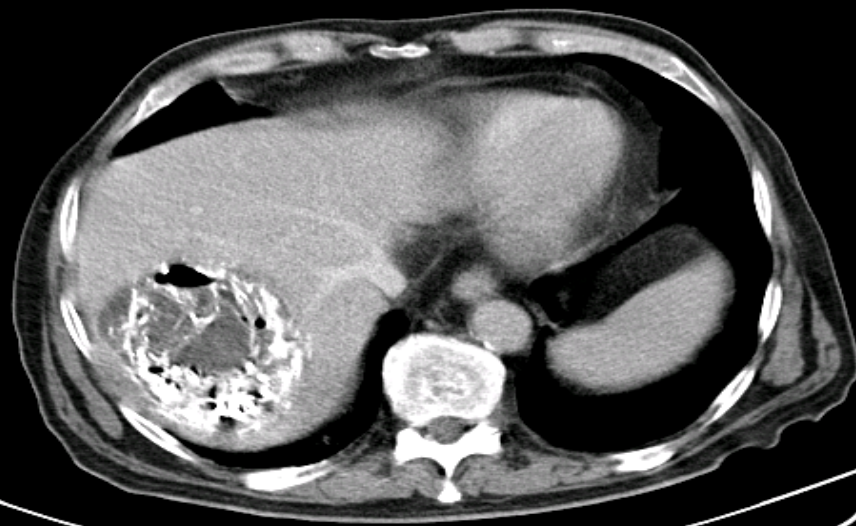
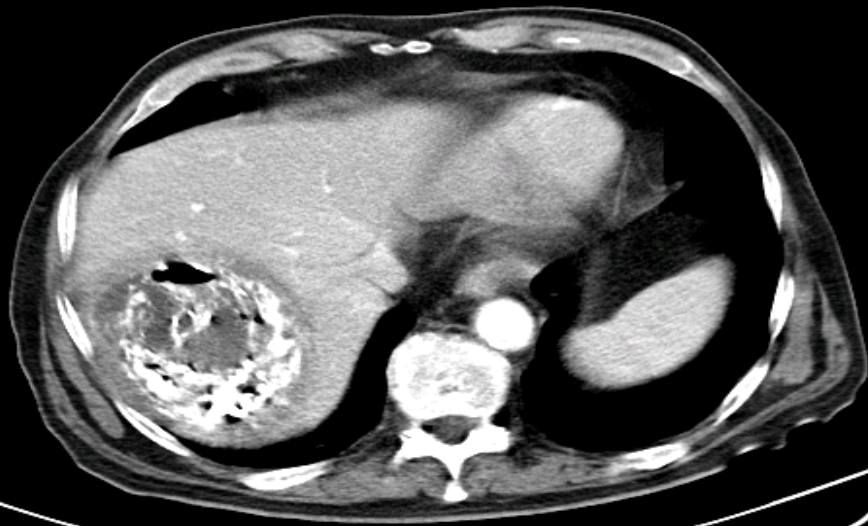
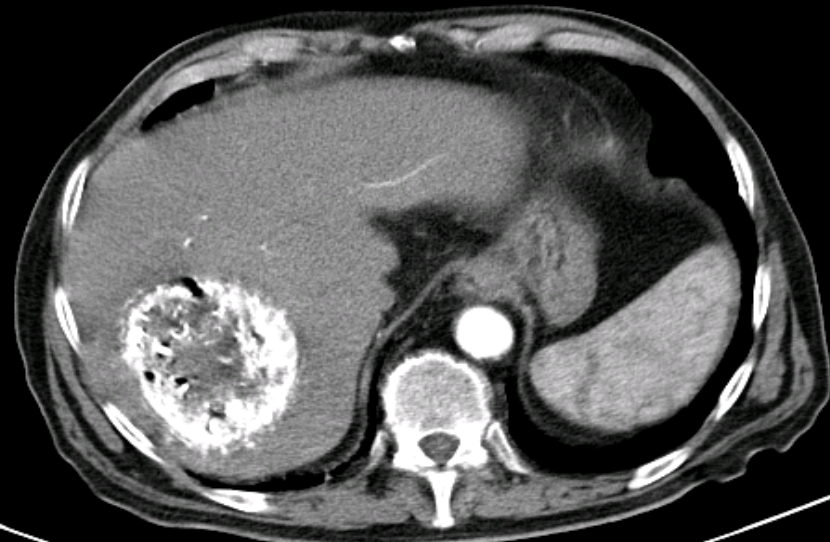
### **CHEMOEMBOLIZATION**

Chemoembolization is recommended for patients with BCLC stage B , multinodular asymptomatic tumors without vascular invasion or extra-hepatic spread (evidence 1ii A; recommendation 1 A ).

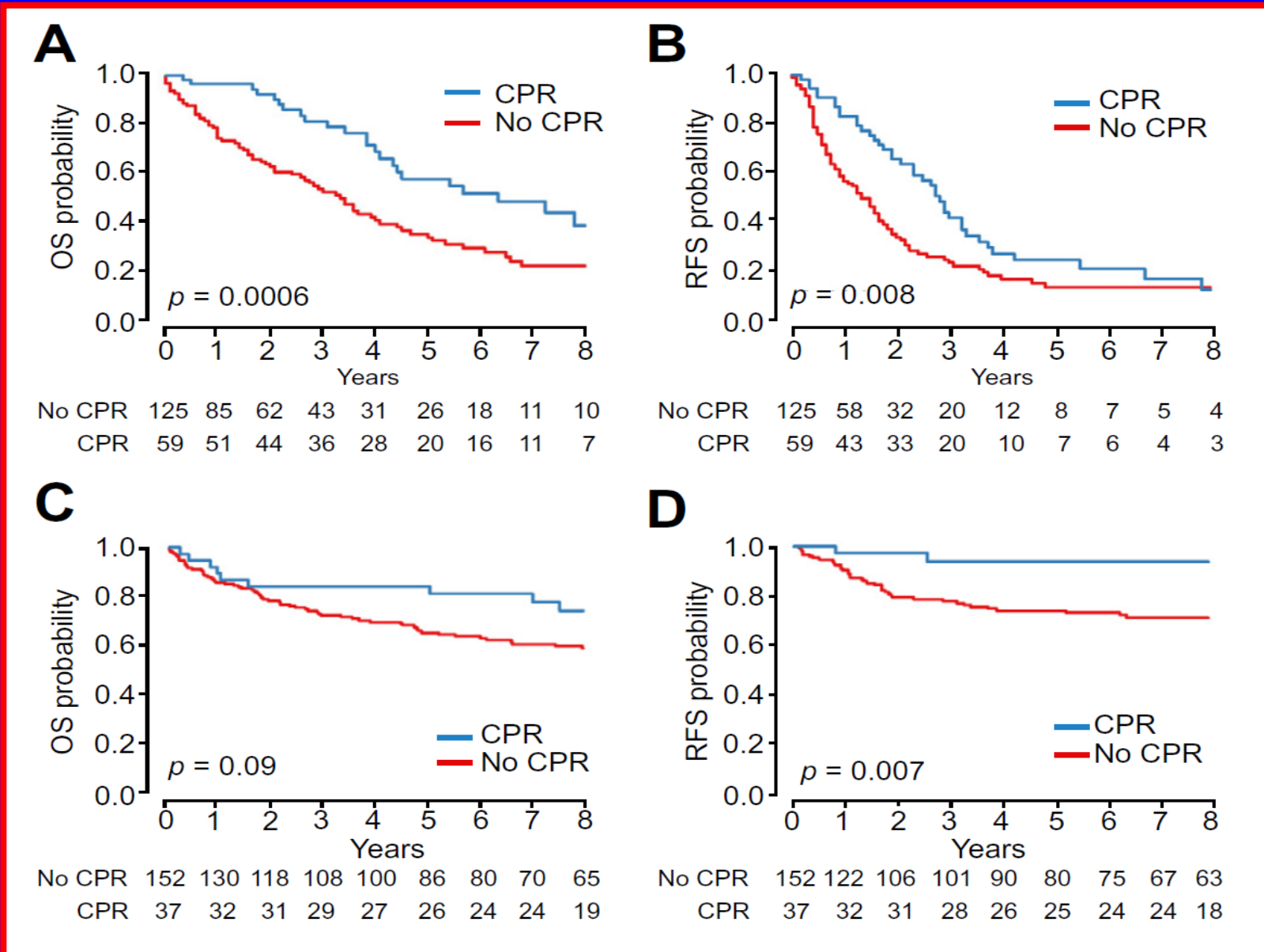
Chemoembolization is discouraged in patients with decompensated liver disease, macroscopic invasion or extrahepatic spread (evidence 1 ii A; recommendation 1 B) .



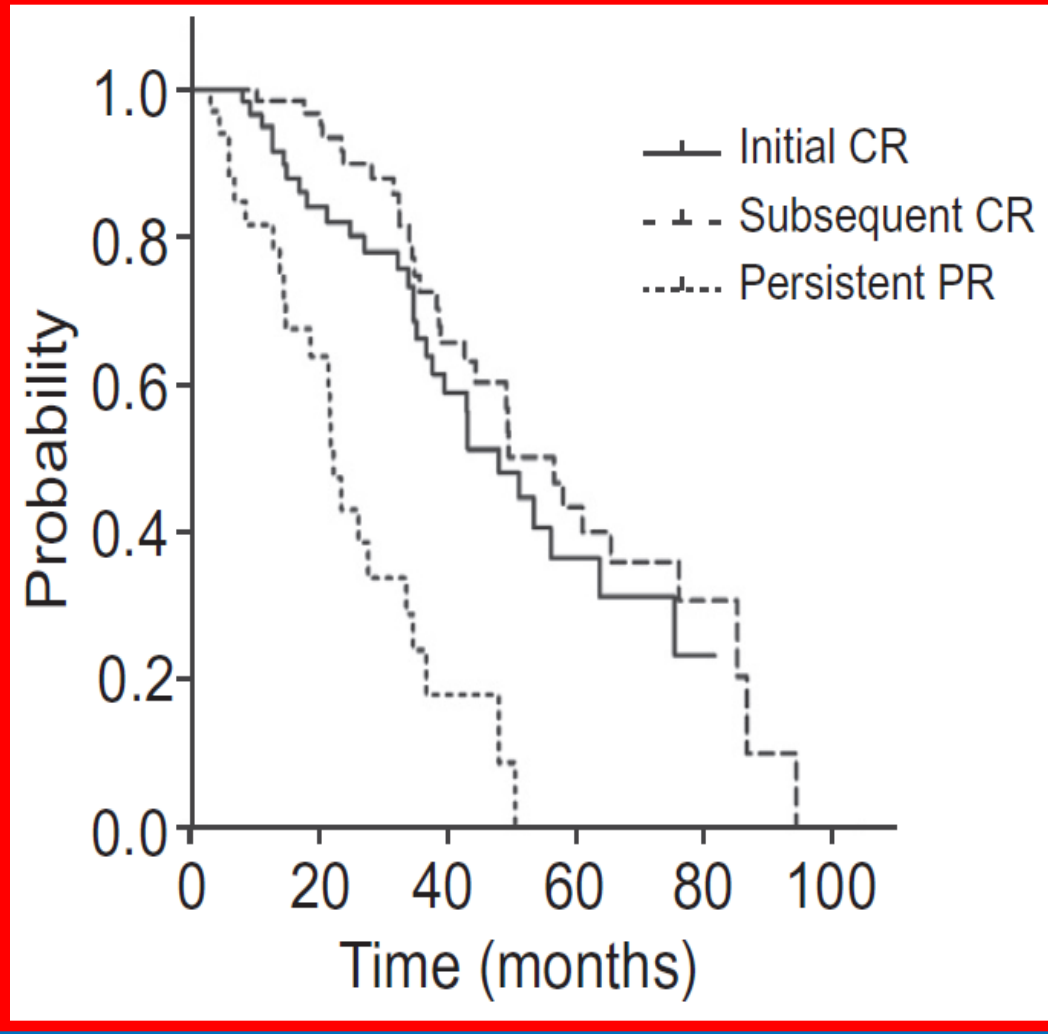
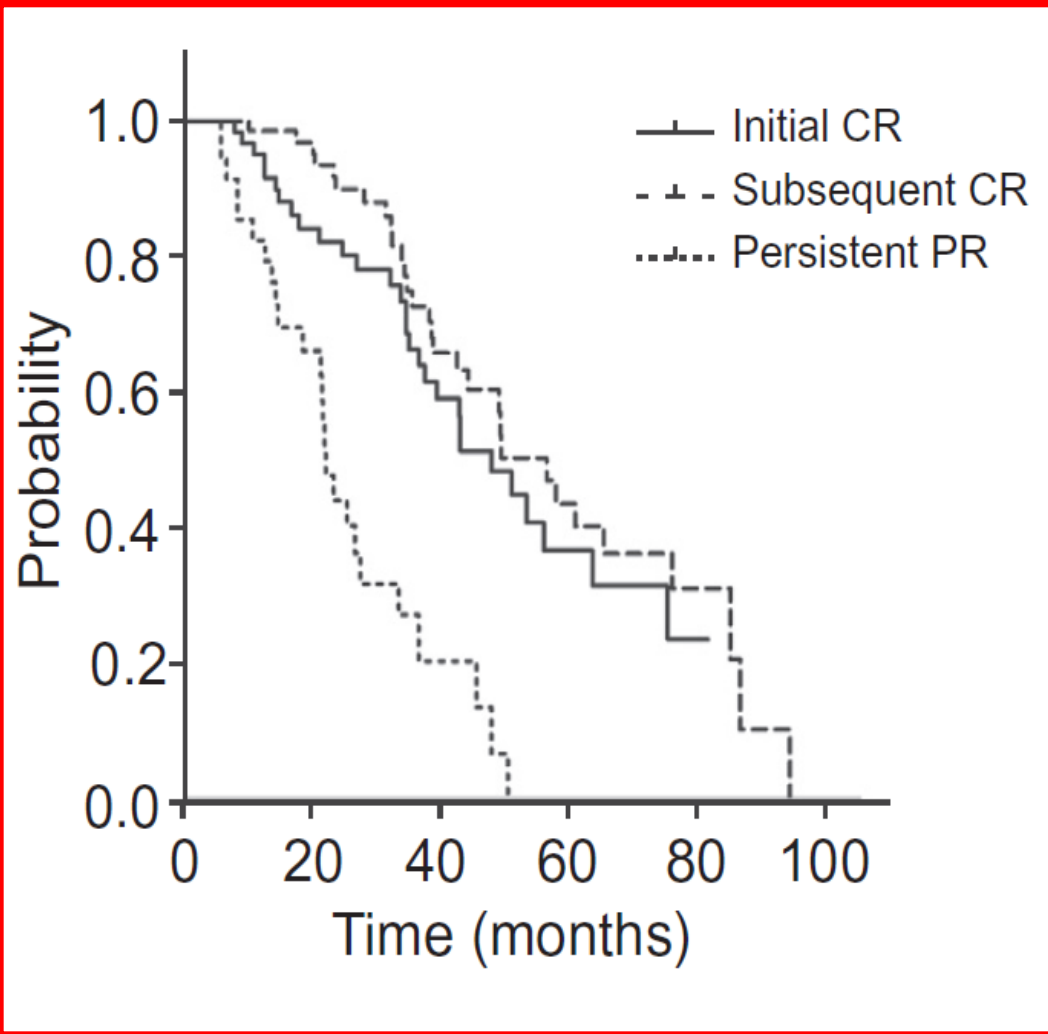




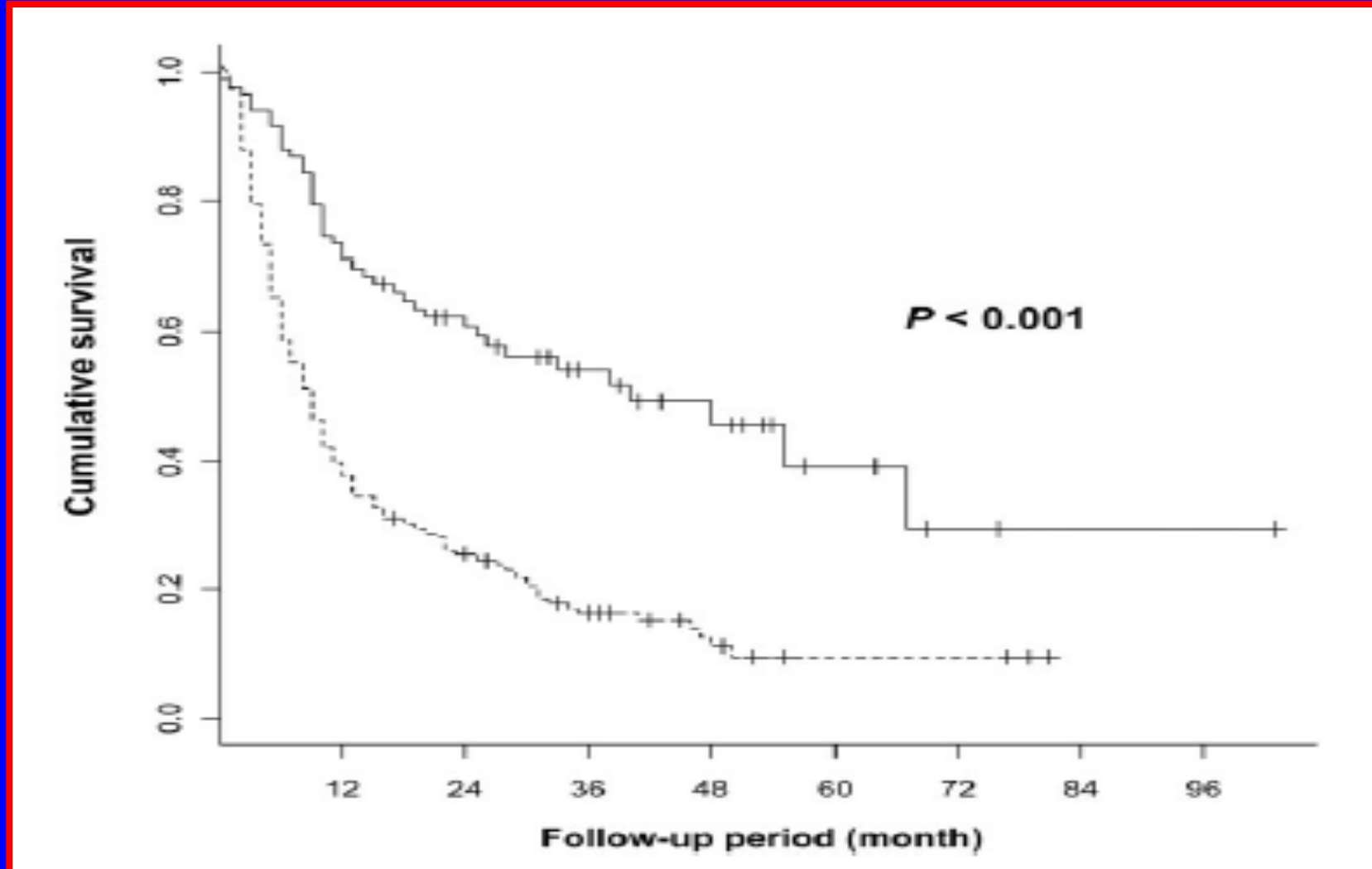
# La risposta patologica dopo TACE e la resezione e il trapianto



# Modalità di risposta e sopravvivenza in 332 HCC trattati con TACE : La sopravvivenza dopo CR iniziale o successiva era simile .



Tassi di sopravvivenza in una serie di pazienti con HCC >10 cm sottoposti a resezione chirurgica ( 84 casi ) o TACE ( 267 casi):Sopravvivenza a 5 anni : 39,8% per resezione vs 9,7% per TACE)



# Meta-analisi di RFA + TACE nel trattamento dell'HCC

Ref.	Treatment	No. of patients	Recurrence- free survival rate			Overall survival rate			
			1 yr	3 yr	5 yr	1 yr	2 yr	3 yr	5 yr
Peng <i>et al</i> <sup>[14]</sup>	TACE+RFA	69	80.00%	45.00%	40.00%	94.00%	NA	69.00%	46.00%
	RFA	70	64.00%	18.00%	18.00%	82.00%		47.00%	36.00%
Cheng <i>et al</i> <sup>[15]</sup>	TACE+RFA	96	NA	NA	58.00%	83.00%	NA	55.00%	31.00%
	RFA	100			42.00%	67.00%		32.00%	8.00%
Yang <i>et al</i> <sup>[16]</sup>	TACE+RFA	24	29.00%	NA	NA	68.00%	NA	NA	NA
	RFA	12	34.70%			57.00%			
Shibata <i>et al</i> <sup>[18]</sup>	TACE+RFA	46	71.30%	48.80%	NA	100.00%	100.00%	84.80%	NA
	RFA	43	74.30%	29.70%		100.00%	88.80%	84.50%	
Morimoto <i>et al</i> <sup>[20]</sup>	TACE+RFA	19	67.00%	NA		100.00%	93.00%	93.00%	NA
	RFA	18	56.00%	28.00%		89.00%	89.00%	80.00%	
Kang <i>et al</i> <sup>[22]</sup>	TACE+RFA	19	NA	NA	NA	84.20%	42.10%	36.80%	NA
	RFA	18				66.10%	22.20%	16.70%	
Shen <i>et al</i> <sup>[23]</sup>	TACE+RFA	18	63.90%	50.00%	NA	87.50%	NA	73.30%	NA
	RFA	16	30.00%	18.70%		52.20%		20.40%	
Zhang <i>et al</i> <sup>[24]</sup>	TACE+RFA	15	NA	NA	NA	100.00%	NA	NA	NA
	RFA	15				80.00%			

Ni JY *et al.* WJG 2013



## **EASL–EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma**

European Association for the Study of the Liver\*,  
European Organisation for Research and Treatment of Cancer

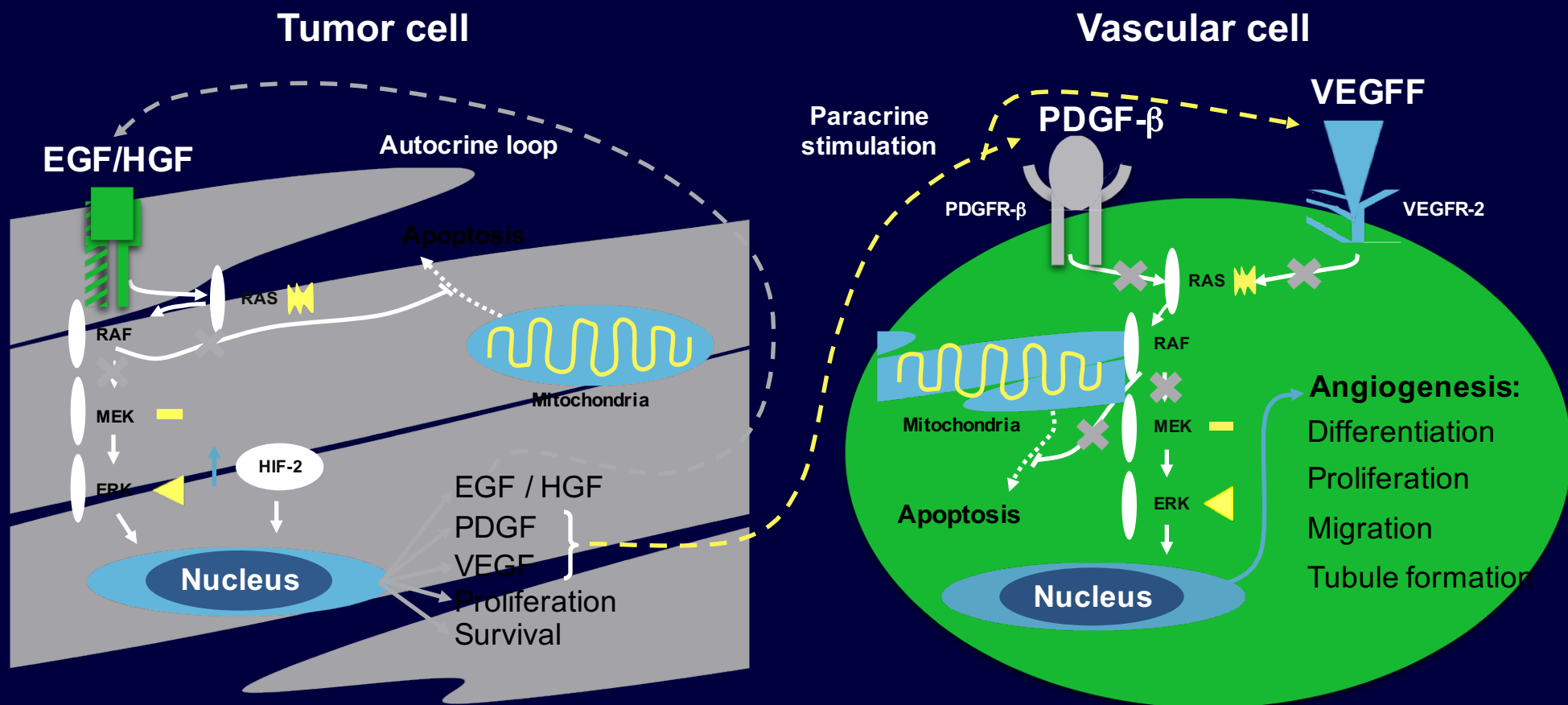
### **SYSTEMIC THERAPIES**

Sorafenib is the standard systemic therapy for HCC. It is indicated for patients with well-preserved liver function ( Child-Pugh class A) and with advanced tumor ( BCLC C ) or those tumors progressing upon loco-regional therapies (evidence 1i A; recommendation 1 A ).

There are no clinical or molecular biomarkers available to identify the best responders to sorafenib (evidence 1A; recommendation 2 A ).

# Targeted Therapy: Sorafenib

Multispecific, blocks tyrosine kinase receptors regulating tumor proliferation and angiogenesis



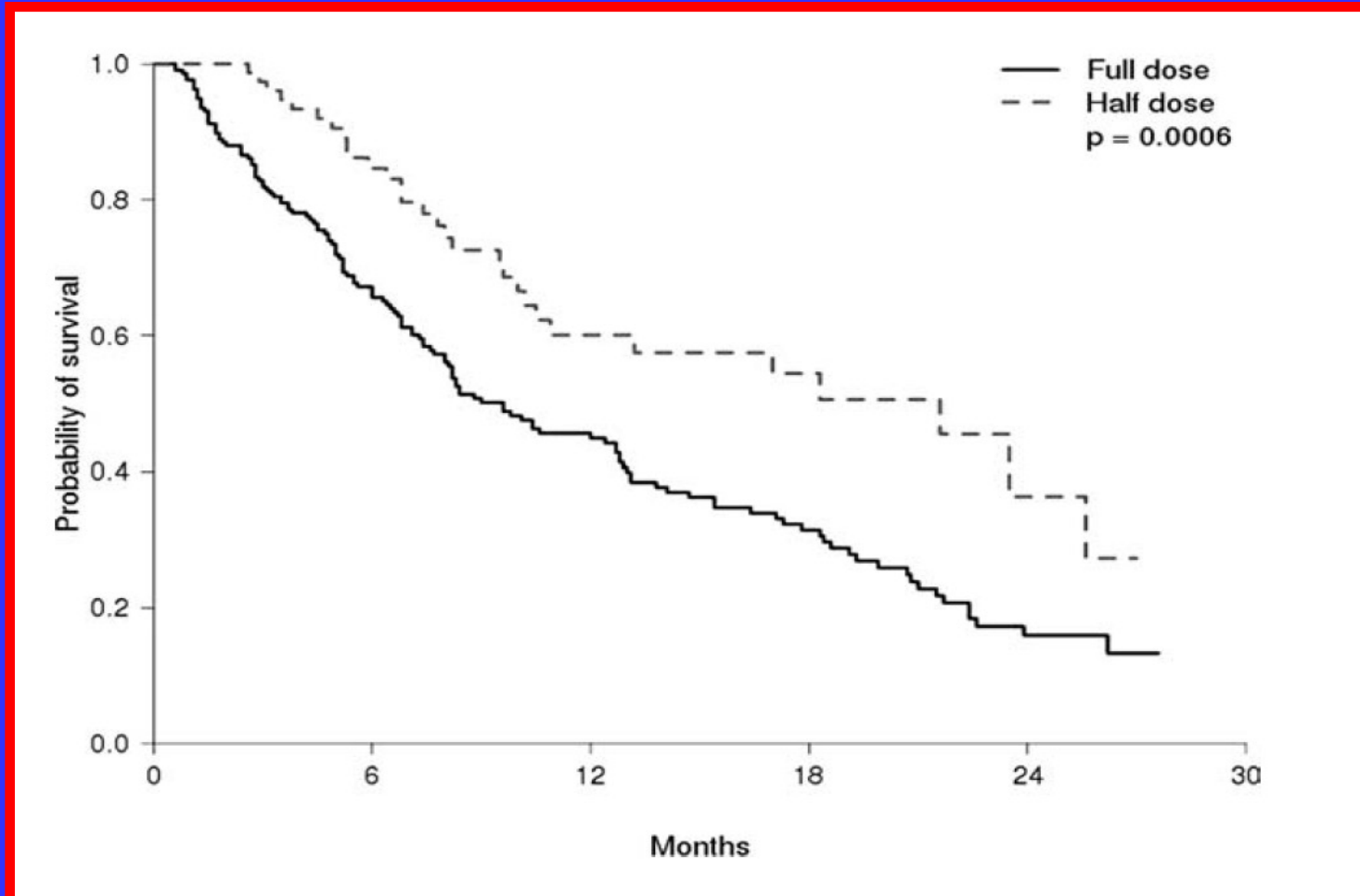
# Randomized Controlled Trials of Sorafenib in Advanced Hepatocellular Carcinoma

Study Characteristics	SHARP Study <sup>1</sup>	Asia Study <sup>2</sup>
Median age	65 yrs	51 yrs
BCLC-B stage	18%	4%
Previous treatments	67%	na
HBV etiology of cirrhosis	19%	71%
<u>TTP (control)</u>	5.5 mo (2.8 mo)	2.8 mo (1.4 mo)
<u>Median survival (control)</u>	10.7 mo (7.9 mo)	6.5 mo (4.2 mo)
Grade 3/4 toxicity	30%	24%

**Treatment-emergent adverse events in the 296 HCC patients treated with sorafenib: multicenter study in Italy**

<b>Adverse Event*</b>	<b>Any Grade</b>	<b>Grade 1/2</b>	<b>Grade 3/4</b>
Overall, no. (%)	269 (91)	136 (46)	133 (45)
Constitutional symptoms, no. (%)			
Fatigue	195 (66)	121 (41)	74 (25)
Weight loss	115 (39)	97 (33)	18 (6)
Dermatological events, no. (%)			
Hand-foot skin reaction	82 (28)	57 (19)	25 (9)
Rash	15 (5)	8 (3)	7 (2)
Gastrointestinal events, no. (%)			
Diarrhea	103 (35)	85 (29)	18 (6)
Nausea/vomiting	34 (11)	25 (8)	9 (3)
Constipation	18 (6)	18 (6)	0
Stomatitis	17 (6)	17 (6)	0
Bleeding	26 (9)	10 (3)	16 (5)
Arterial hypertension	53 (18)	32 (11)	21 (7)
Any cardiovascular event	15 (5)	8 (3)	7 (2)

# Overall survival according to the prevalent dose of sorafenib



Iavarone et al Hepatology 2011

# Beyond Sorafenib: New Agents in HCC

Agent	Molecular Targets	Phase	Response, %	Median OS, Mos	Median TTP, Mos	Median PFS, Mos	Safety: Grade 3-4 AEs, %
Doxorubicin ± sorafenib <sup>[1]</sup>		II	PR: 4.0	13.7	6.4	6.0	Fatigue (6) Hand-foot skin reaction (6.4)
Sunitinib <sup>[2]</sup>	VEGFR, PDGFR, FLT3, KIT, RET	III	CR+PR: <7	7.9	4.1	3.6	Significant toxicities; discontinued
Brivanib <sup>[3]</sup>	VEGFR, FGFR	II	ORR: 4.3	9.8	1.8	2.0	HTN (7.3) Diarrhea (6.5) Headache (4.3)
Linifanib (ABT-869) <sup>[4]</sup>	VEGFR, PDGFR	II	ORR: 6.8	9.7	3.7	NR	HTN (18) Fatigue (14)
Cabozantinib (XL184) <sup>[5]</sup>	c-MET, VEGFR2	II	PR: 9.0	NR	NR	4.2	Hand-foot syndrome (15) Diarrhea (9) TP (9)
Tivantinib (ARQ197) <sup>[6]</sup>	c-MET	II	NR	MET high: 7.2	MET high: 2.9	MET high: 2.4	Neutropenic sepsis (4.2)

1. Abou-Alfa GK, et al. JAMA. 2010;304:2154-2160. 2. Cheng A, et al. ASCO 2011. Abstract 4000. 3. Finn RS, et al. Clin Cancer Res. 2012;18:2090-2098. 4. Toh H, et al. ASCO 2010. Abstract 4038. 5. Cohn AL, et al. ASCO GI. 2012. Abstract 261. 6. Rimassa, L, et al. ASCO 2012. Abstract 4006.

# Radioembolization indications and contraindications by general consensus

## Indications

### Conventional

(based on retrospective and prospective cohort studies and case-control studies)

Intermediate HCC

Single, multinodular (2-3 or tumor burden <20% of the liver parenchyma)

Child-Pugh A, normal liver function, PS 0

Okuda II, multifocal (bilobar or tumor burden 20%-40% of the liver parenchyma), Child-Pugh B, PS 0, only if good liver function and bilirubin <2 mg/dL

Advanced HCC

No extrahepatic disease, branch or main portal vein invasion, with normal liver function, PS 0

### Investigational

(based on case reports or single-center studies)

Radiation-induced segmentectomy, for patients unfit for ablation or embolization

Radiation-induced hepatectomy associated with tumor treatment, for patients unfit for surgery because of comorbidities, or insufficient remnant liver

Downstaging procedure before resection or transplantation in case of intermediate-advanced HCC (exceeding conventional criteria)



# Radioembolization indications and contraindications by general consensus

## Contraindications

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### Relative

- Renal failure
- Untreated varices at high risk of bleeding

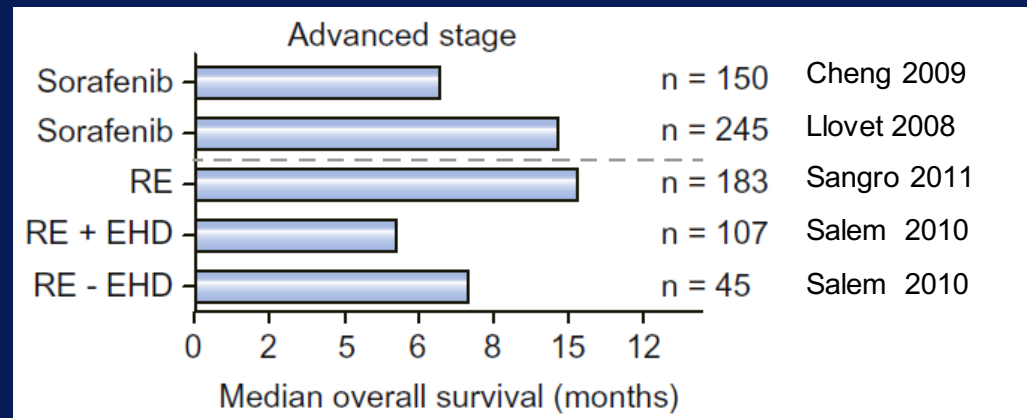
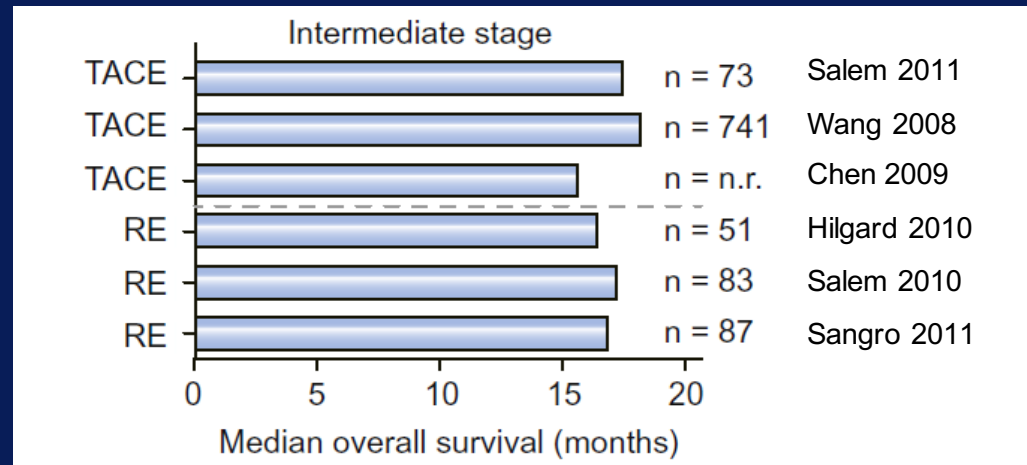
### Absolute

- Technical contraindication to intra-arterial treatment
- Decompensated cirrhosis (CPT  $\geq 8$ , jaundice, encephalopathy, refractory ascites, or hepatorenal syndrome)
- Massive tumor with both lobes involved (tumor burden  $> 75\%$  of liver parenchyma)
- Lung or GI shunts that cannot be corrected

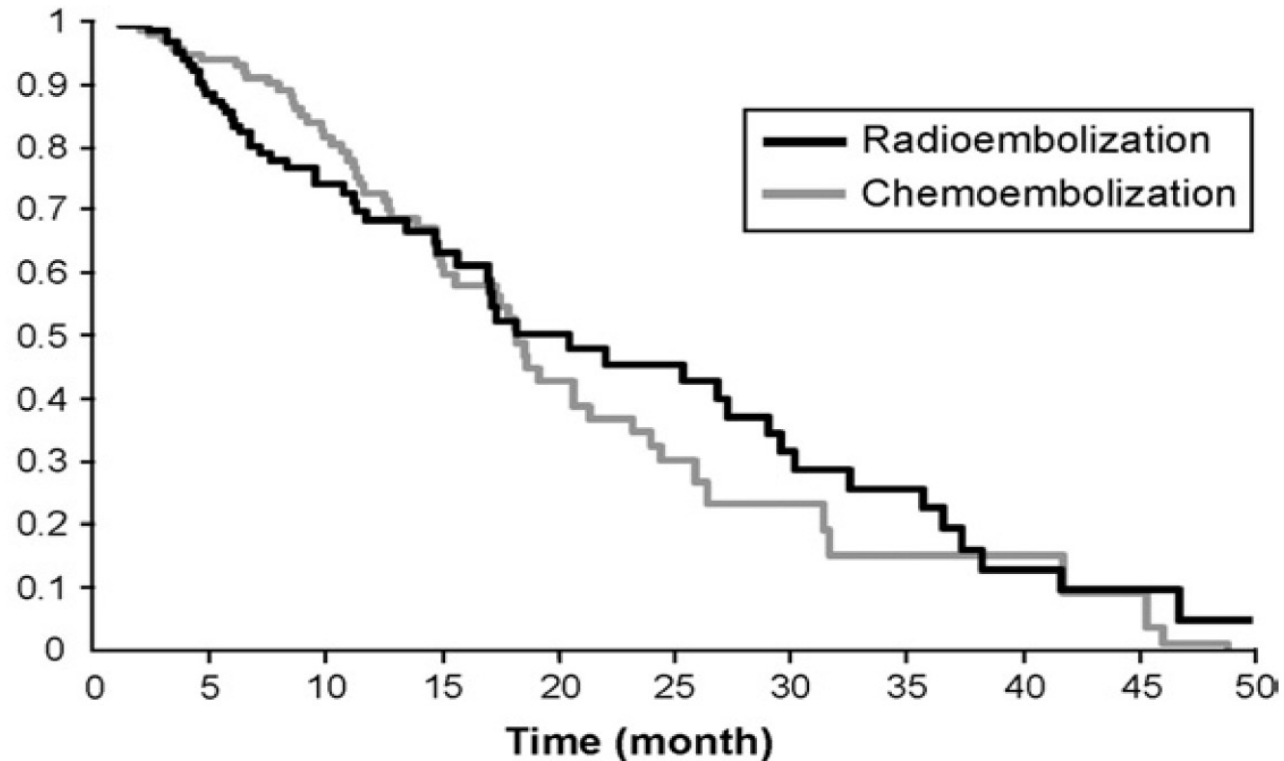
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PS, performance status.

# Y-90 Radioembolization for Hepatocellular Carcinoma



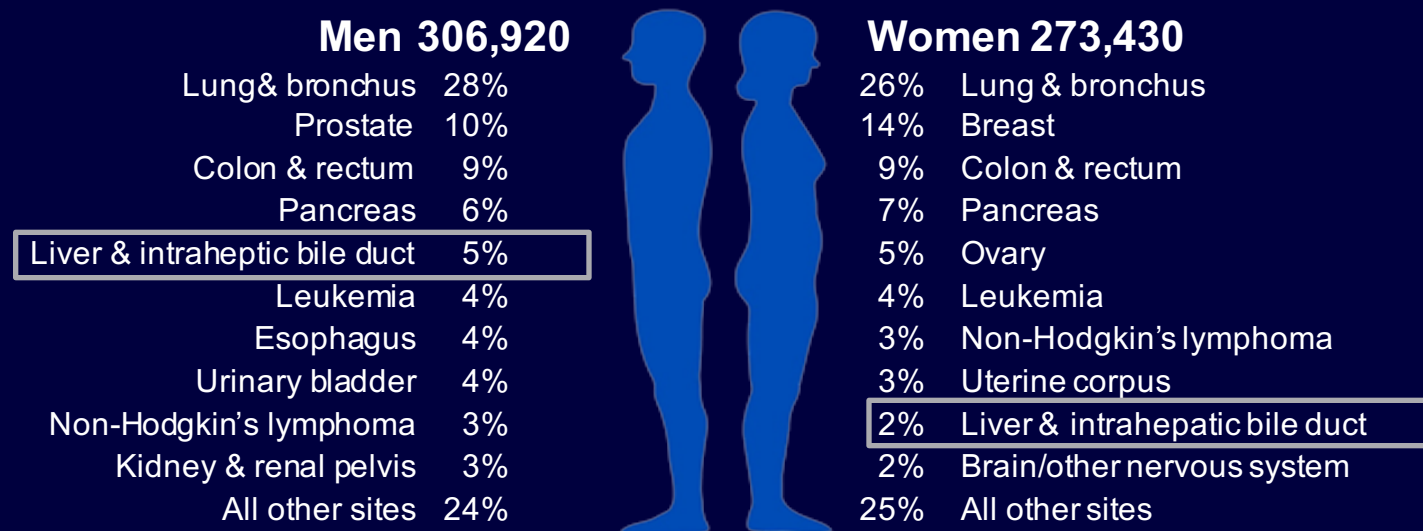
Radioembolization results in longer time-to-progression and reduced toxicity compared with TACE in patients with HCC



Number at risk

Chemoem.	122	79	56	31	18	11	8	5	5	3	0
Radioem.	123	84	54	37	24	19	14	10	5	3	2

# 2013 Estimated US Cancer Deaths



- Liver cancer in 2013 estimated as:
  - The #5 cancer killer in men (up from #7 in 2005)
  - The #9 cancer killer in women (not among top 10 in 2005)

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# Adherence to American Association for the Study of Liver Diseases guidelines for the management of hepatocellular carcinoma: results of an Italian field practice multicenter study

Mauro Borzio\*<sup>1,2</sup>, Fabio Fornari<sup>3</sup>, Ilario De Sio<sup>4</sup>, Angelo Andriulli<sup>5</sup>, Fulvia Terracciano<sup>5</sup>, Giancarlo Parisi<sup>6</sup>, Gianpiero Francica<sup>7</sup>, Mario Salvagnini<sup>8</sup>, Massimo Marignani<sup>9</sup>, Andrea Salmi<sup>10</sup>, Fabio Farinati<sup>11</sup>, Alessandra Carella<sup>12</sup>, Claudia Pedicino<sup>1</sup>, Elena Dionigi<sup>1</sup>, Libera Fanigliulo<sup>3</sup>, Massimo Cazzaniga<sup>13</sup>, Barbara Ginanni<sup>14</sup> & Rodolfo Sacco<sup>14</sup>; EpaHCC Group<sup>†</sup>

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<sup>11</sup>Dipartimento di scienze Chirurgiche e Gastroenterologiche, Ospedale Policlinico, Padova, Italy

<sup>12</sup>Unità di Gastroenterologia, Ospedale Sant'Anna, Ferrara, Italy

<sup>13</sup>Dipartimento di Medicina, Ospedale Policlinico, San Donato, Italy

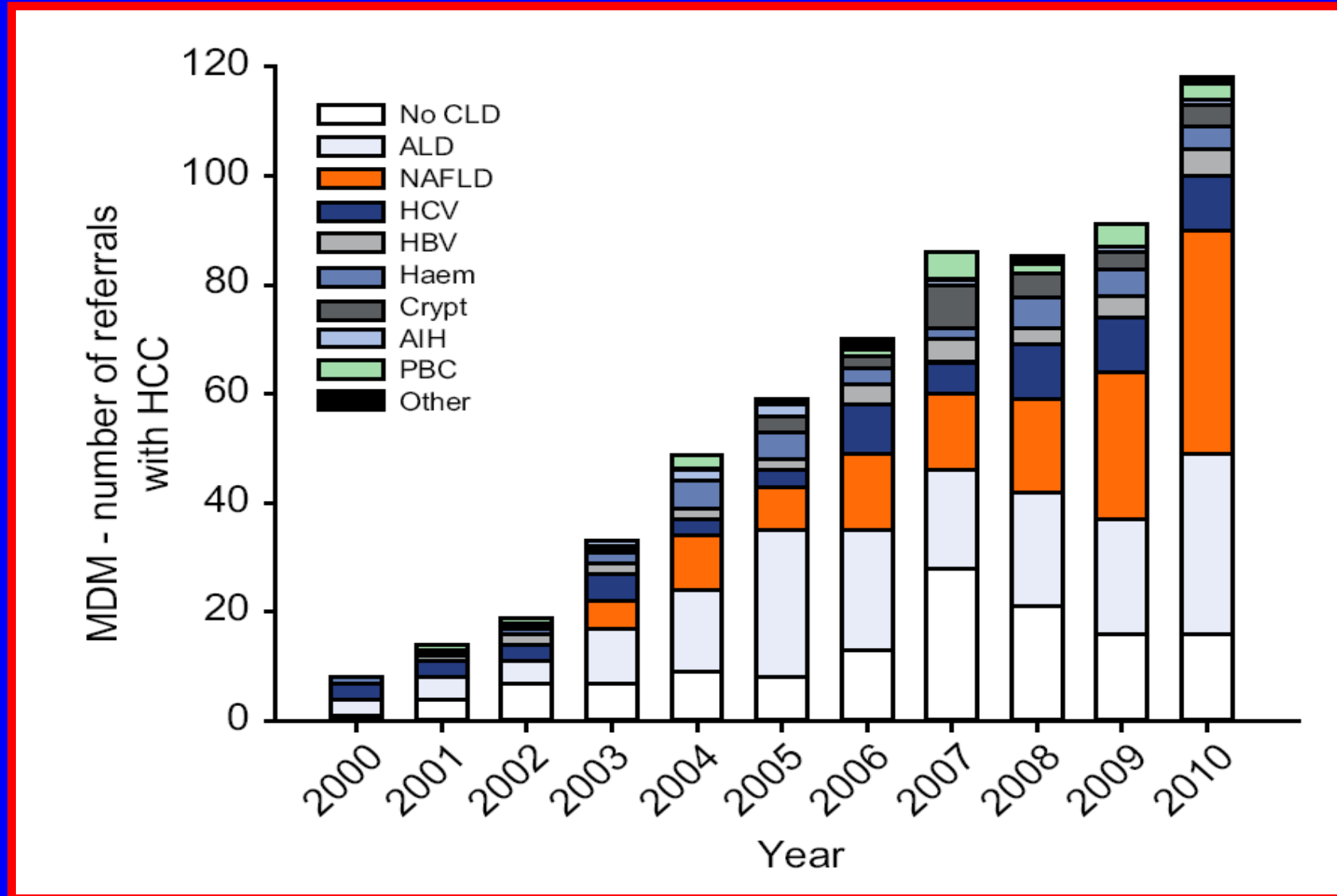
<sup>14</sup>Unità di Gastroenterologia, Ospedale Cisanello, Pisa, Italy

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<sup>†</sup>For a full list of the other members of the EpaHCC Group, please see pages 293–294

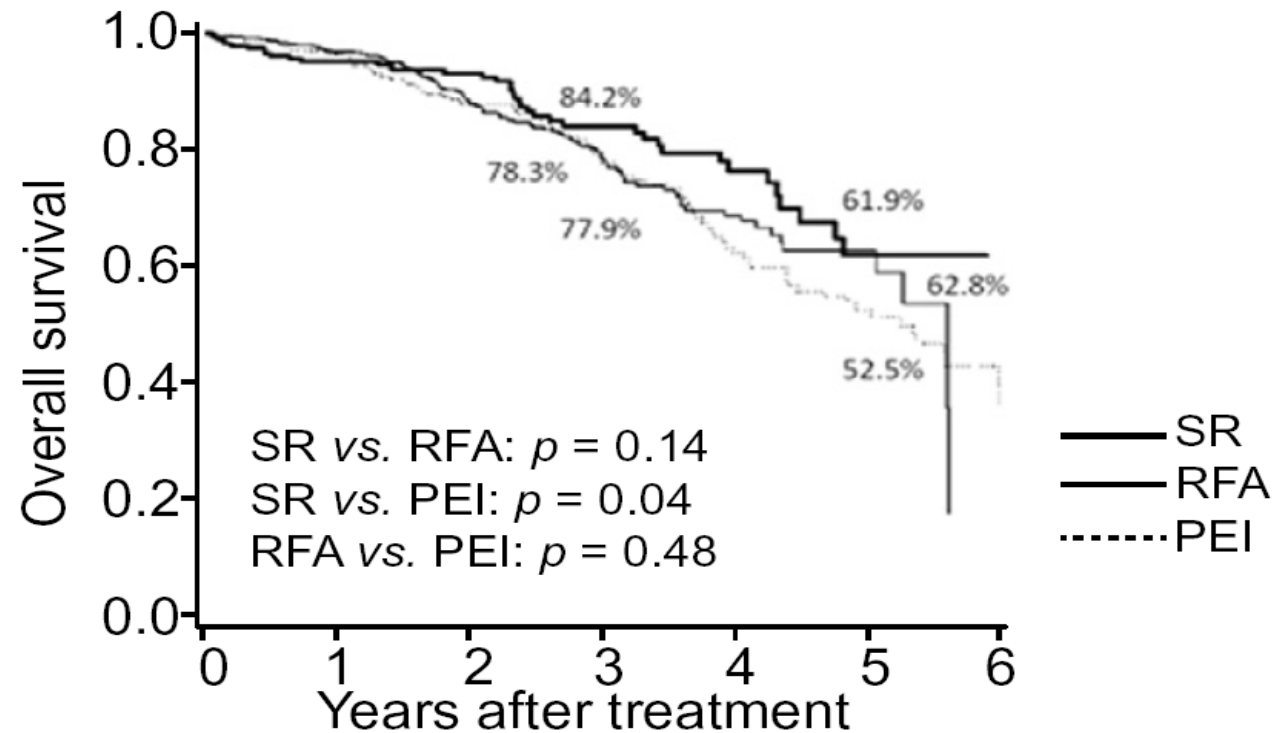
Future Oncology  
Research Article

# Eziologia della epatopatie croniche associate con HCC



Dyson et al J Hepatology 2014

## Sopravvivenza dopo SR, RFA e PEI in Child B, singolo < 2 cm

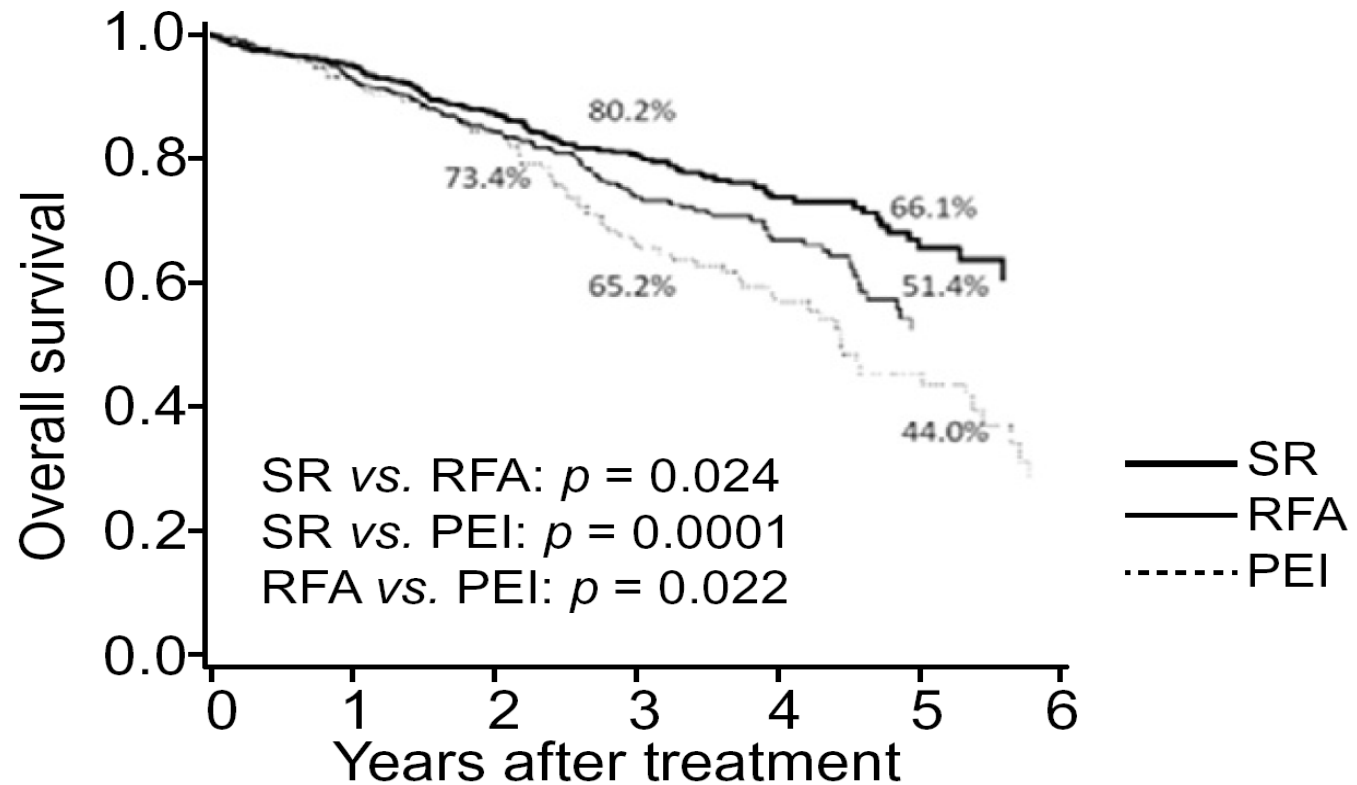


### Patients at risk

SR	279	199	142	85	47	19
RFA	757	511	306	168	70	18
PEI	336	254	180	121	70	44



# Sopravvivenza dopo SR, RFA, PEI in HCC Child B , singolo , 2-3cm

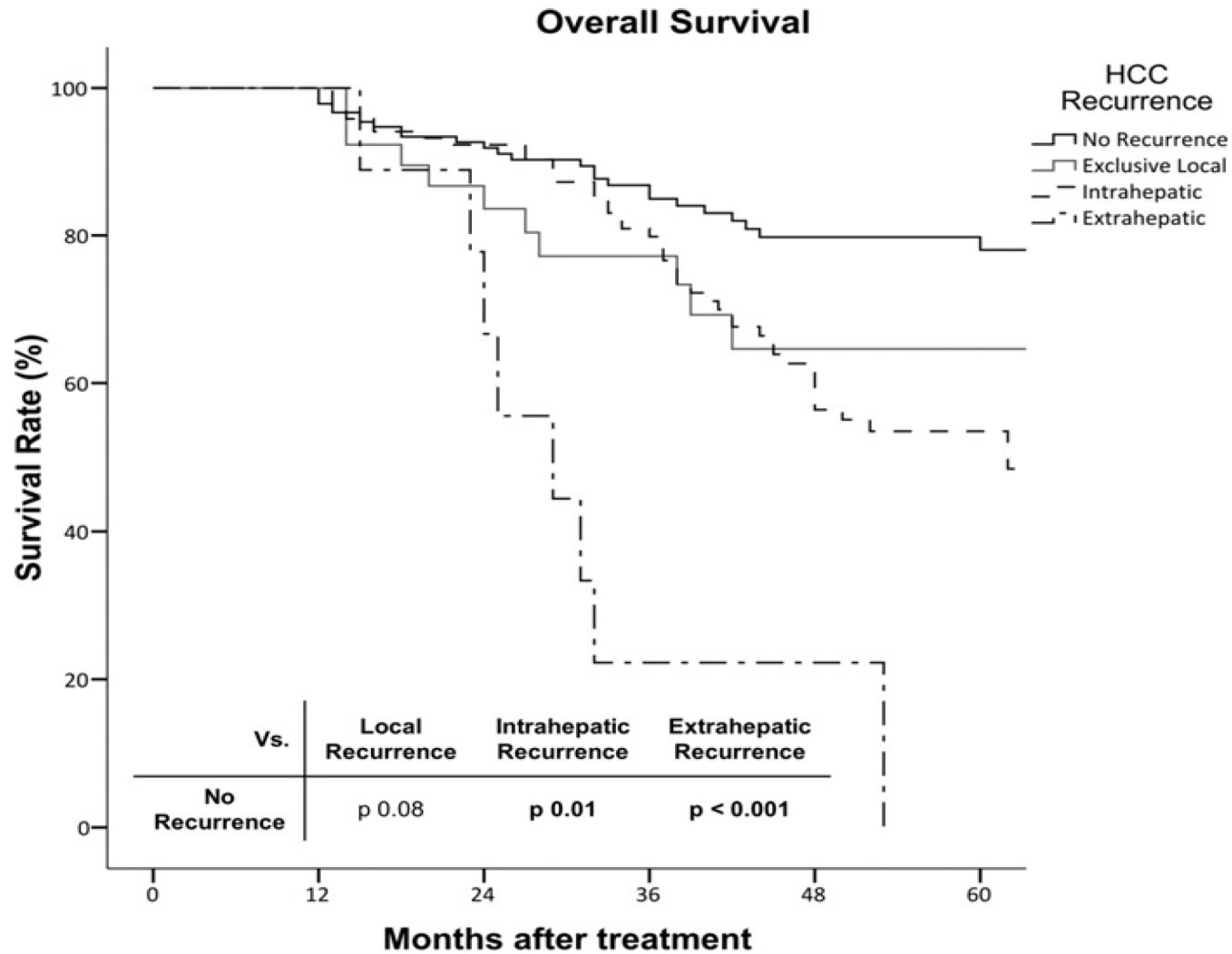


## Patients at risk

SR	838	603	397	260	115	50
RFA	805	528	332	194	94	27
PEI	250	190	128	74	43	25

Hasegawa et al J Hepatology 2013

# Long-term effectiveness of RFTA for solitary small HCC



## Cost-effectiveness of hepatic resection versus percutaneous RFA for early HCC

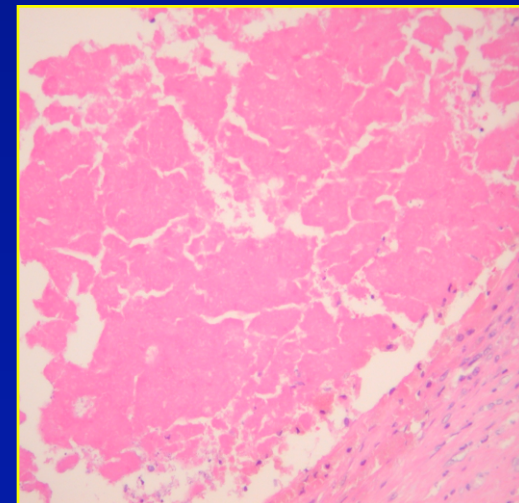
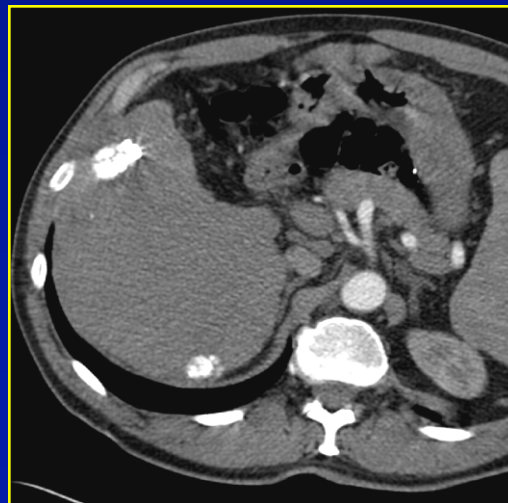
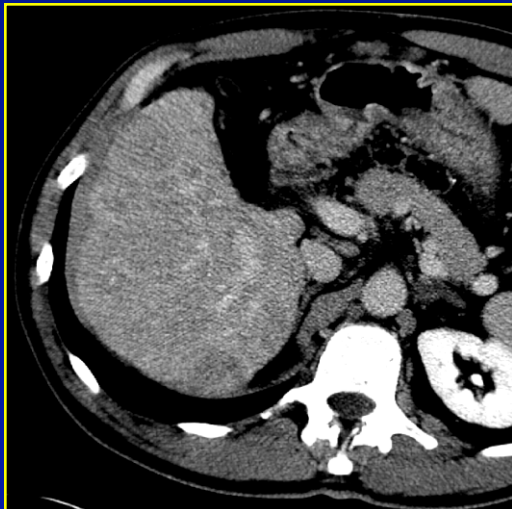
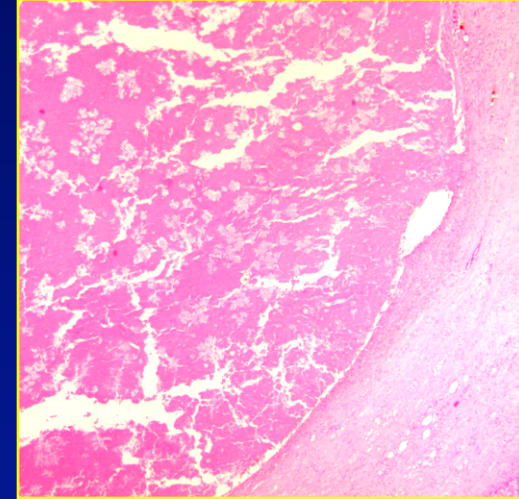
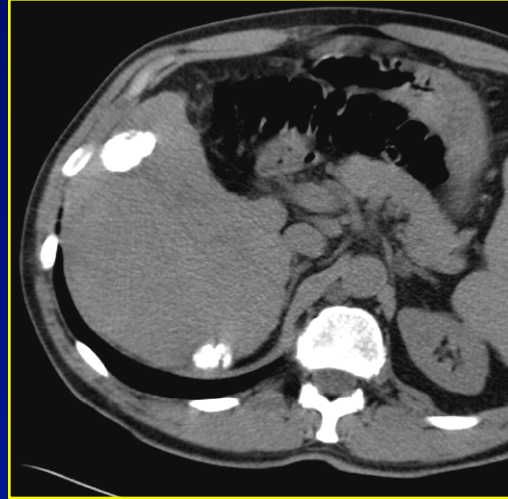
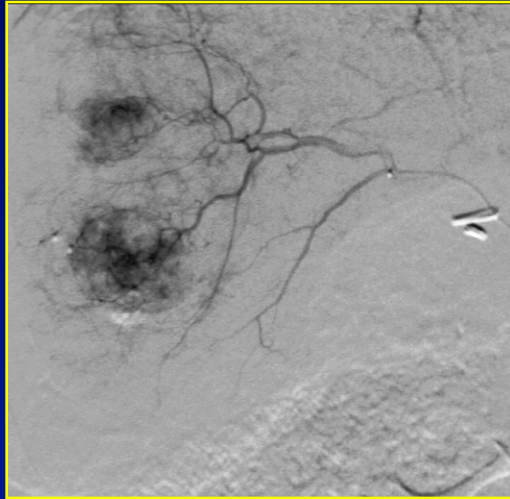
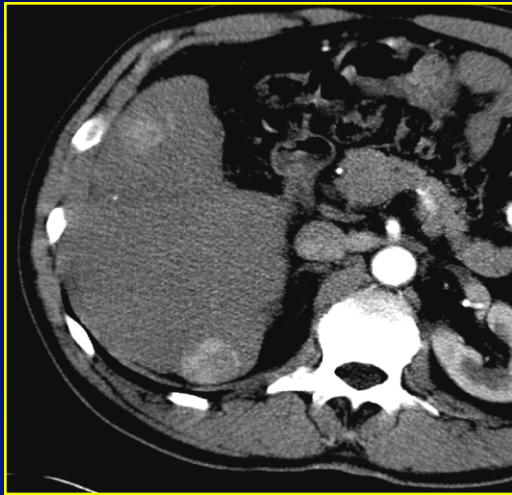
La resezione chirurgica comporta una aspettativa di vita ( a parità di qualità) a costi più elevati rispetto alla RFA ( 1938 euro vs 1181 euro)

Nell' HCC very early la RFA produce una migliore aspettativa di vita a costi più bassi rispetto alla resezione chirurgica

Nei noduli di maggiori dimensioni la resezione chirurgica produce un migliore aspettativa di vita con un migliore rapporto costi-efficacia .

In presenza di 2-3 noduli < 3 cm , l'aspettativa di vita è simile per entrambi i trattamenti ; la RFA si conferma però a costi più bassi .

# Work-up Diagnostico/Terapeutico

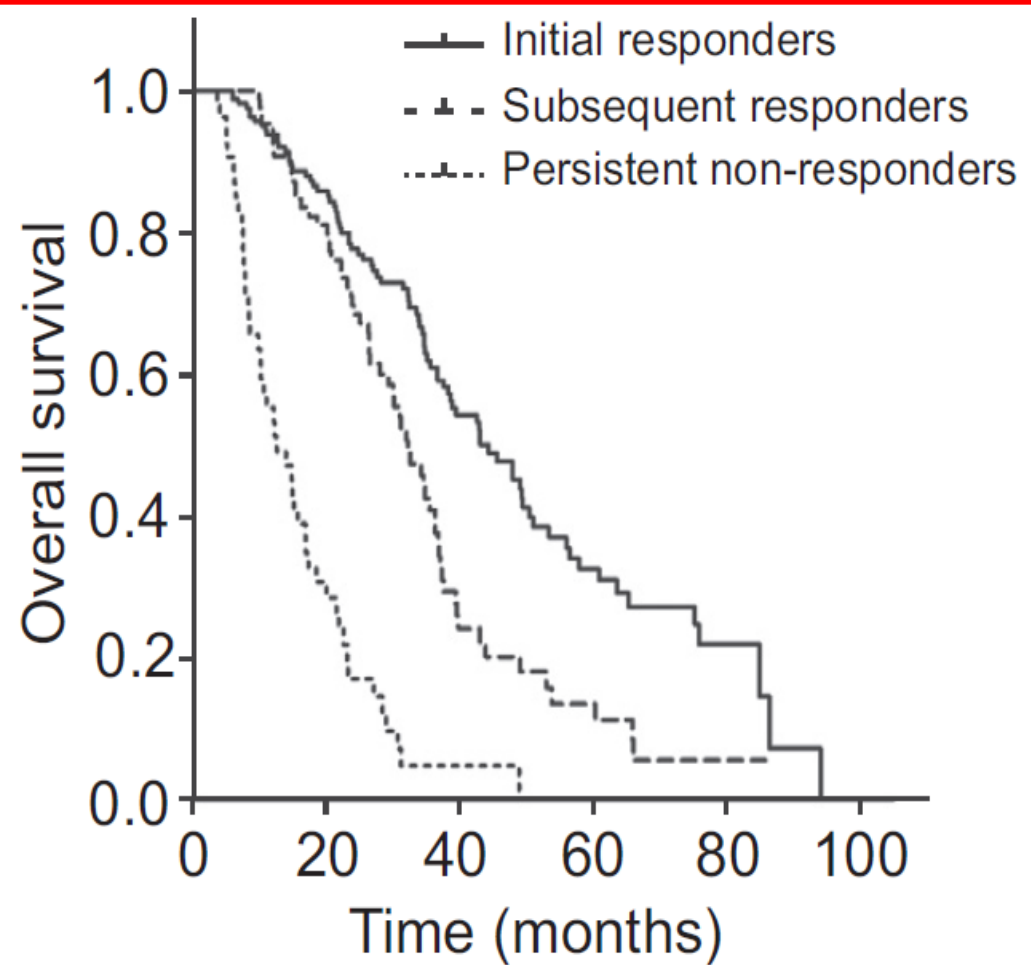
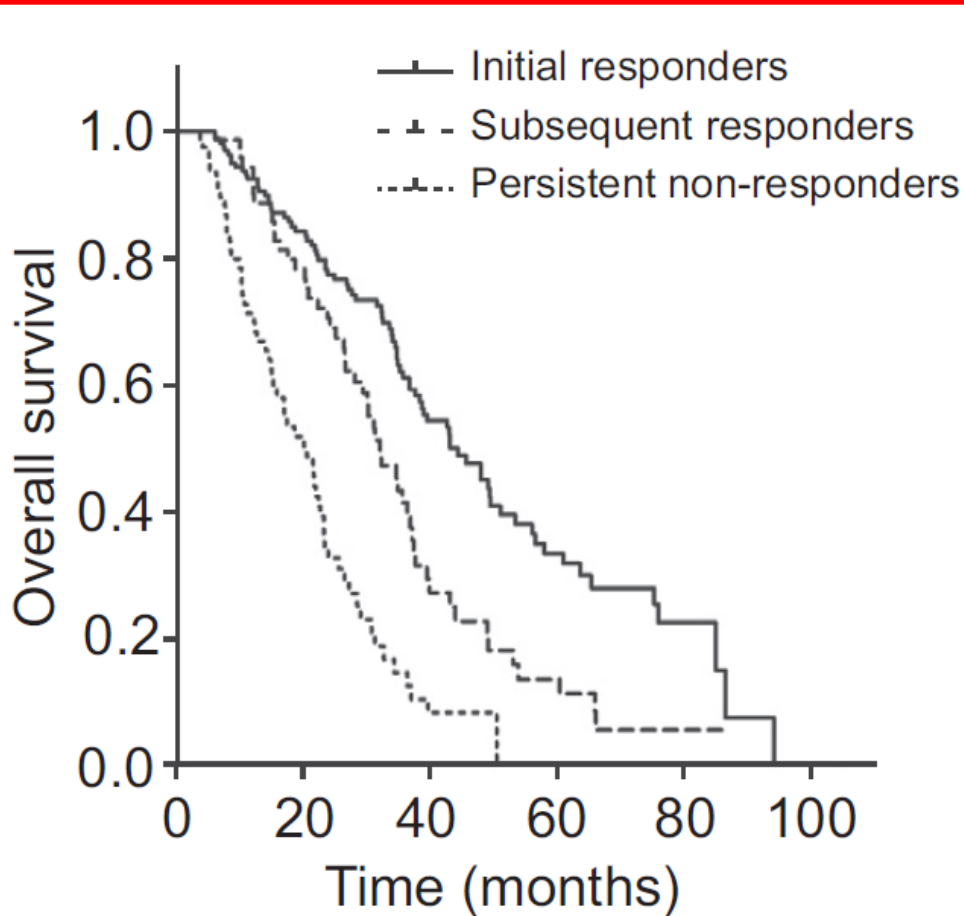


TC

TACE

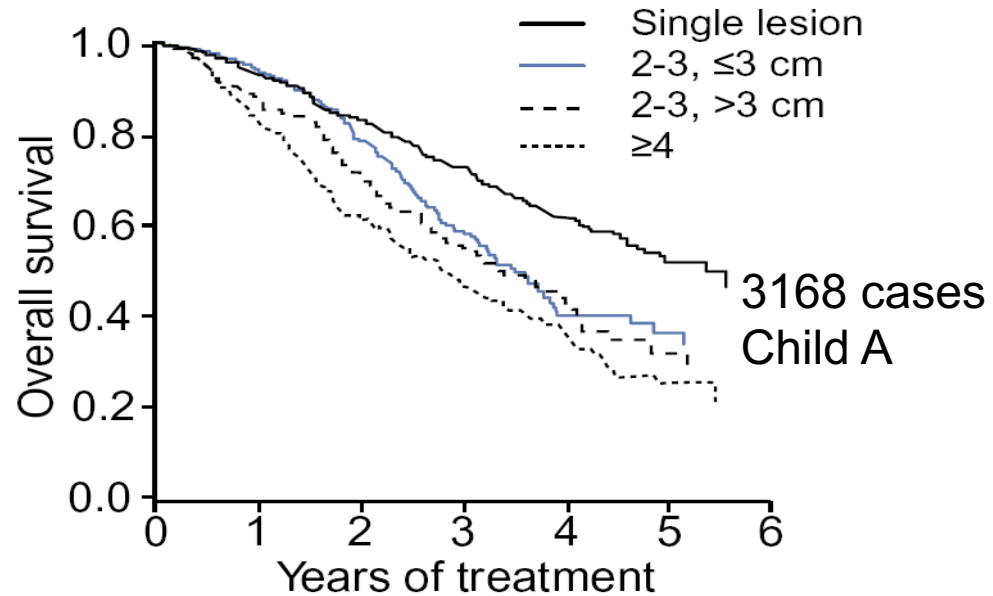
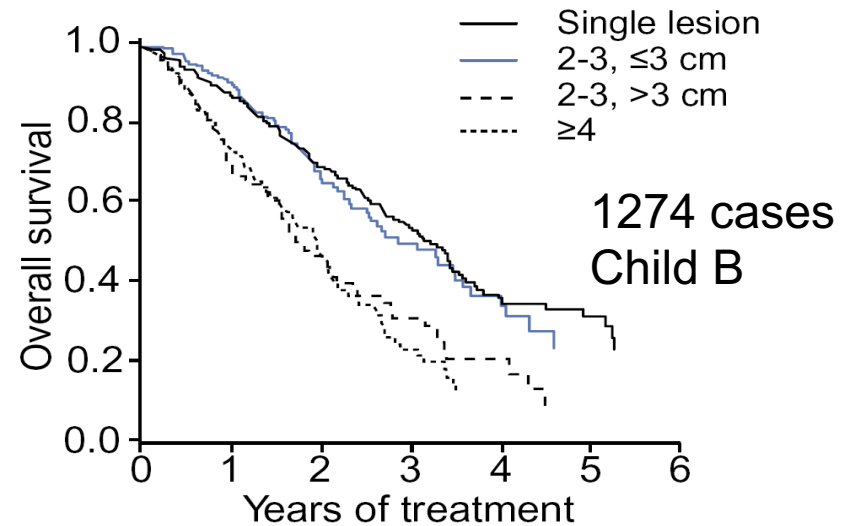
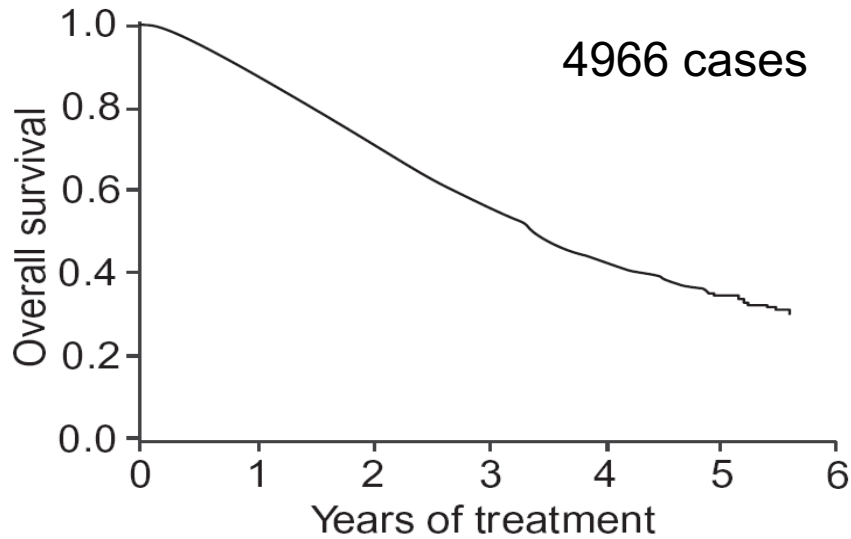
4 – 5 sett

# Sopravvivenza dopo ripetute TACE in 332 pazienti con HCC "intermediate": modalità di risposta EASL and RECIST



# Superselective TACE for HCC

Takayasu et al J Hepatol 2012





# Analisi multivariata dei fattori predittivi di sopravvivenza dopo ripetuti trattamenti con TACE : 332 pazienti con HCC "intermediate"

Variable	EASL model		mRECIST model	
	HR	p value	HR	p value
Initial response				
Non-responder	1.0		1.0	
Responder	0.69 (0.48-1.00)	0.050	0.71 (0.50-1.01)	0.055
Best response				
Non-responder	1.0		1.0	
Responder	0.45 (0.30-0.66)	<0.001	0.24 (0.16-0.36)	<0.001
Serum AFP, ≥200 ng/ml	1.66 (1.23-2.23)	<0.001	1.72 (1.27-2.32)	<0.001
Tumor number, ≥4	1.66 (1.22-2.26)	<0.001	1.77 (1.30-2.41)	<0.001
Size of largest tumor, ≥5 cm	1.27 (0.85-1.90)	0.238	1.33 (0.89-1.98)	0.168
Size of 2 <sup>nd</sup> largest tumor, ≥5 cm	0.96 (0.64-1.46)	0.862	0.83 (0.55-1.26)	0.391

Numbers in parentheses are the 95% confidence intervals.

AFP, alpha fetoprotein; HR, hazard ratio.



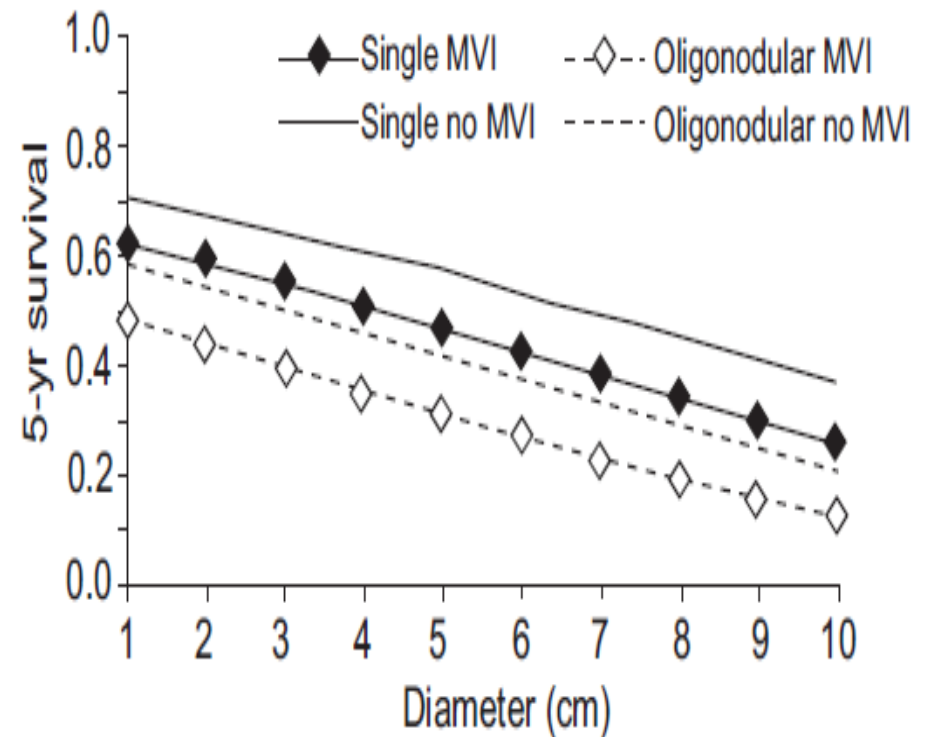
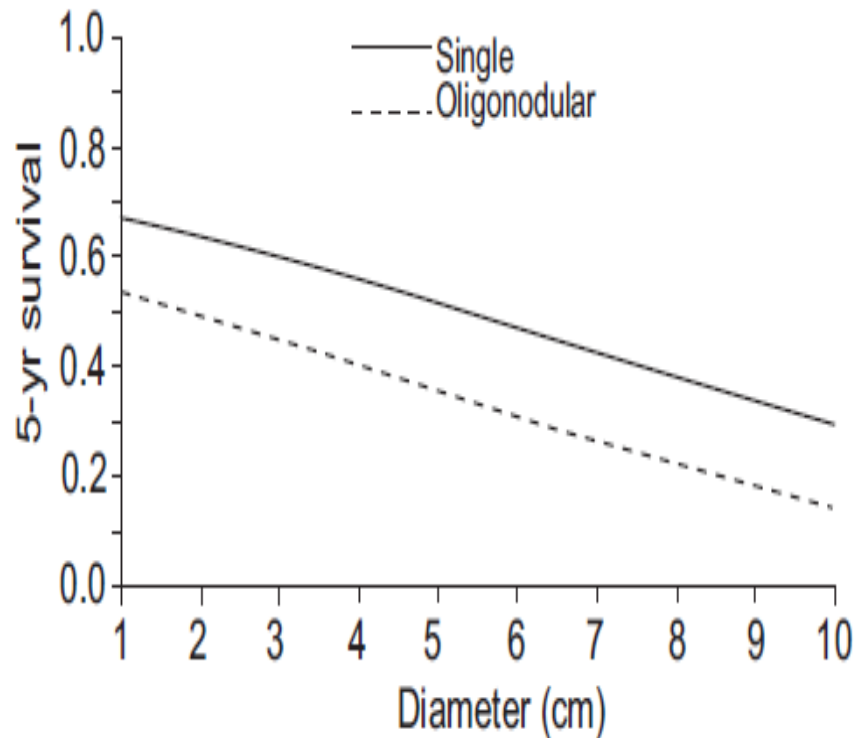
# Impatto clinico della diagnosi di epatocarcinoma (HCC)



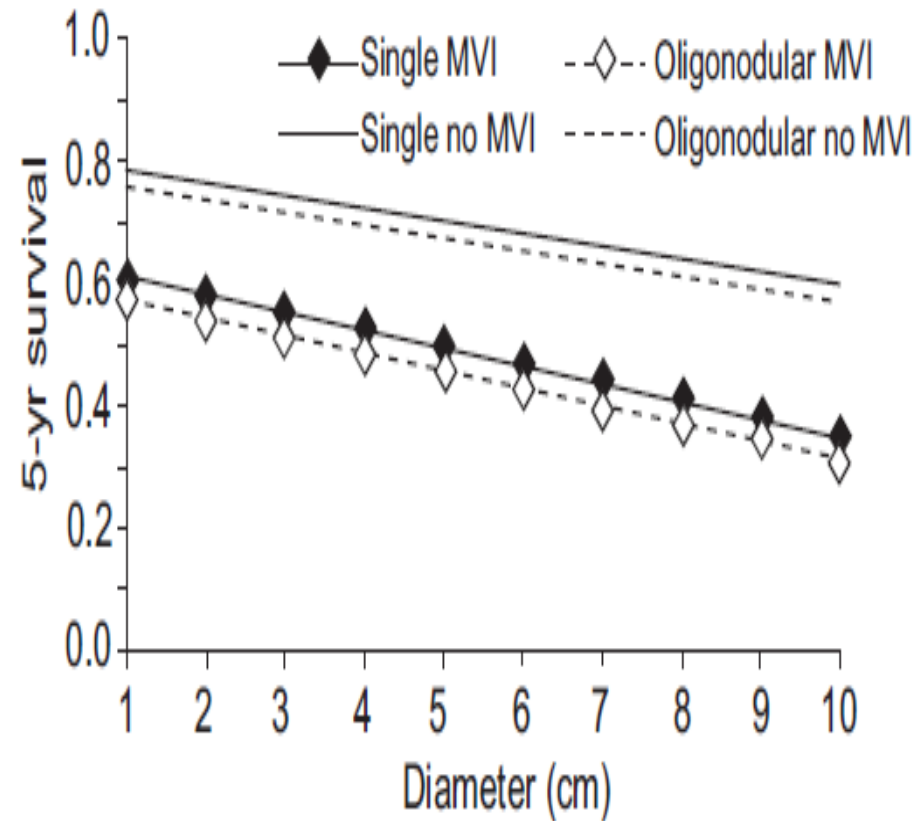
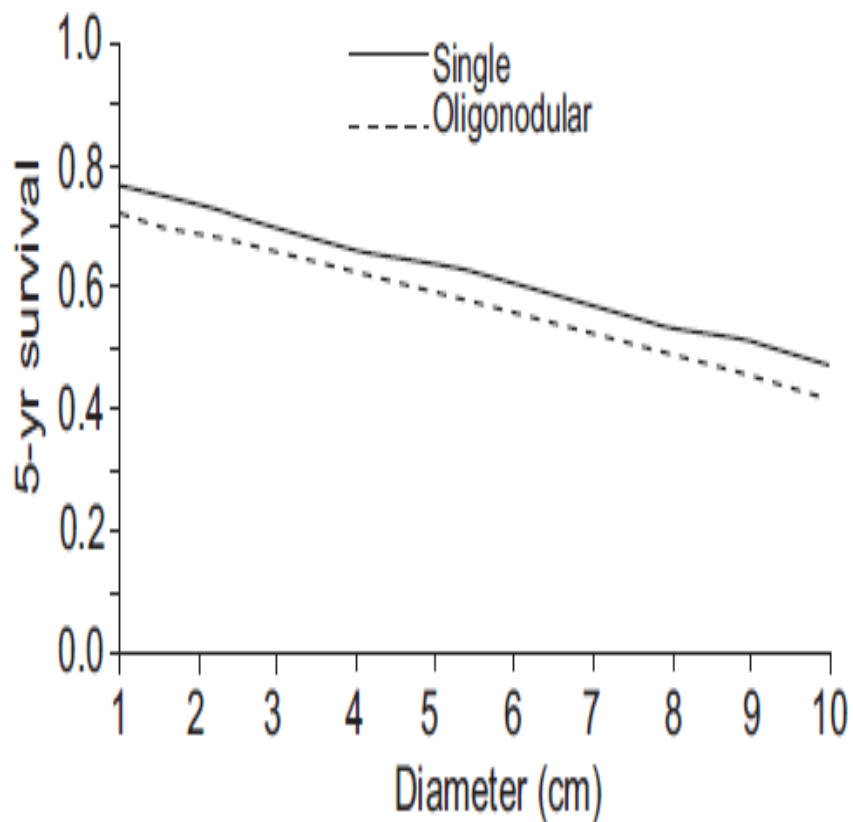
**Fabio Fornari**

U.O. Complessa di Gastroenterologia ed Epatologia  
Ospedale "G. da Saliceto" - Piacenza

# Sopravvivenza a 5 anni post-LT rispetto a numero, diametro e MVI



# Sopravvivenza a 5 anni dopo HR rispetto a numero , diametro e invasione microvascolare ( MVI) in 1028 pazienti cirrotici con HCC





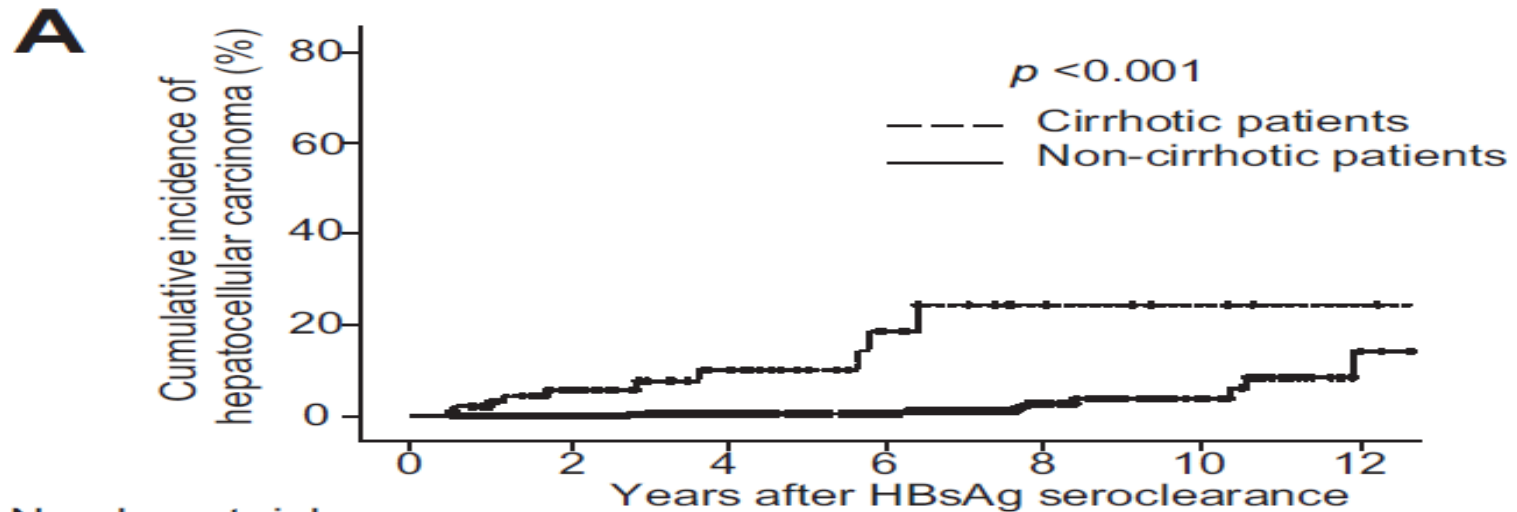
# Radiofrequency ablation of very early HCC

218 patients with single HCC  $\leq$  2cm, Child A

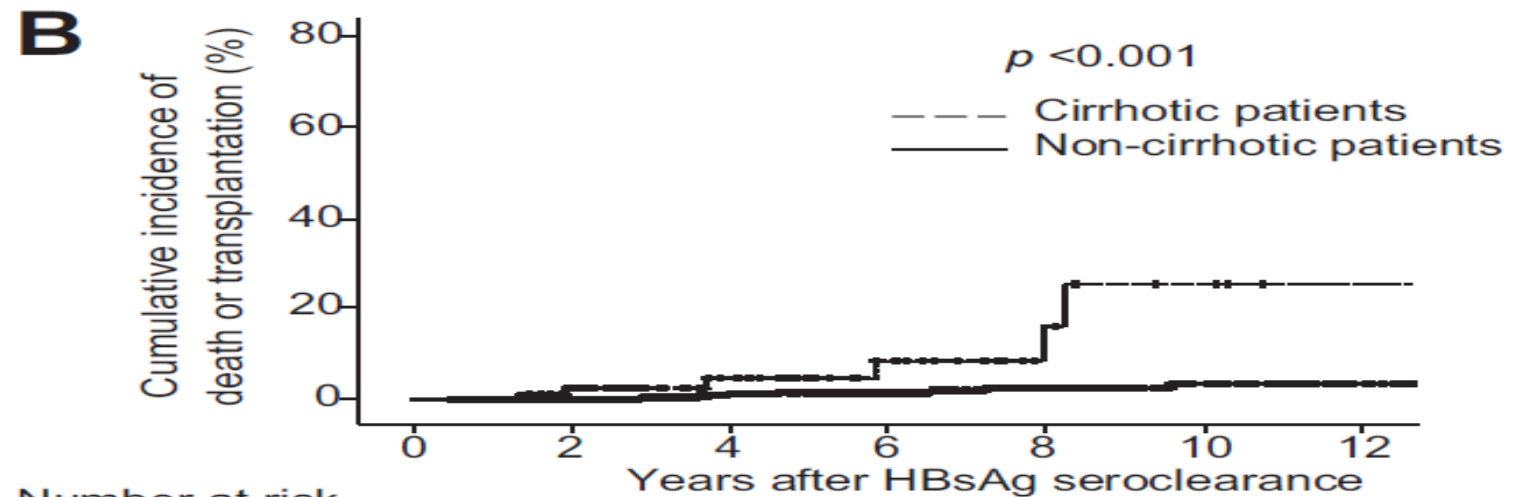
Complete radiologic necrosis after 1 session	<b>98.1%</b>
Treatment failure	<b>1.8%</b>
Local recurrence (Follow-up 6-134 mo)	<b>0.9%</b>
Survival rates (3y - 5y)	<b>76% - 55%</b>
Survival rates of the potentially operable patients (3y - 5y)	<b>89%- 68%</b>
Survival rates of the potentially inoperable patients (3y - 5y)	<b>75% - 47%</b>
Disease-free survival rates (3y - 5y)	<b>26% - 20%</b>

RFTA as the treatment of choice for patients with single HCC < 2cm in diameter

# Incidenza cumulativa di HCC e mortalità o trapianto rispetto alla presenza di cirrosi

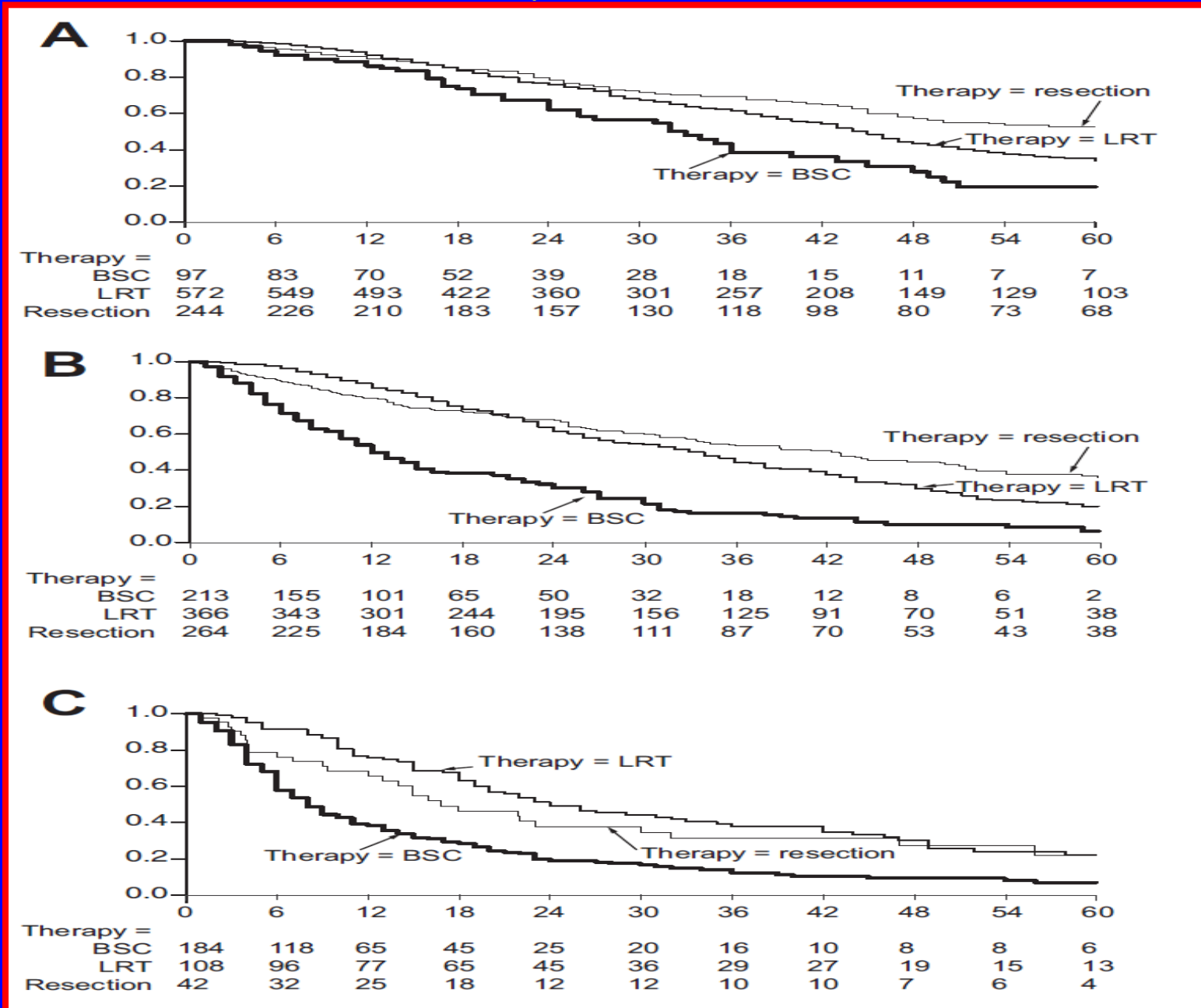


Number at risk	0	2	4	6	8	10	12
Non-cirrhosis	731	523	305	202	106	49	14
Cirrhosis	98	66	35	16	7	4	2

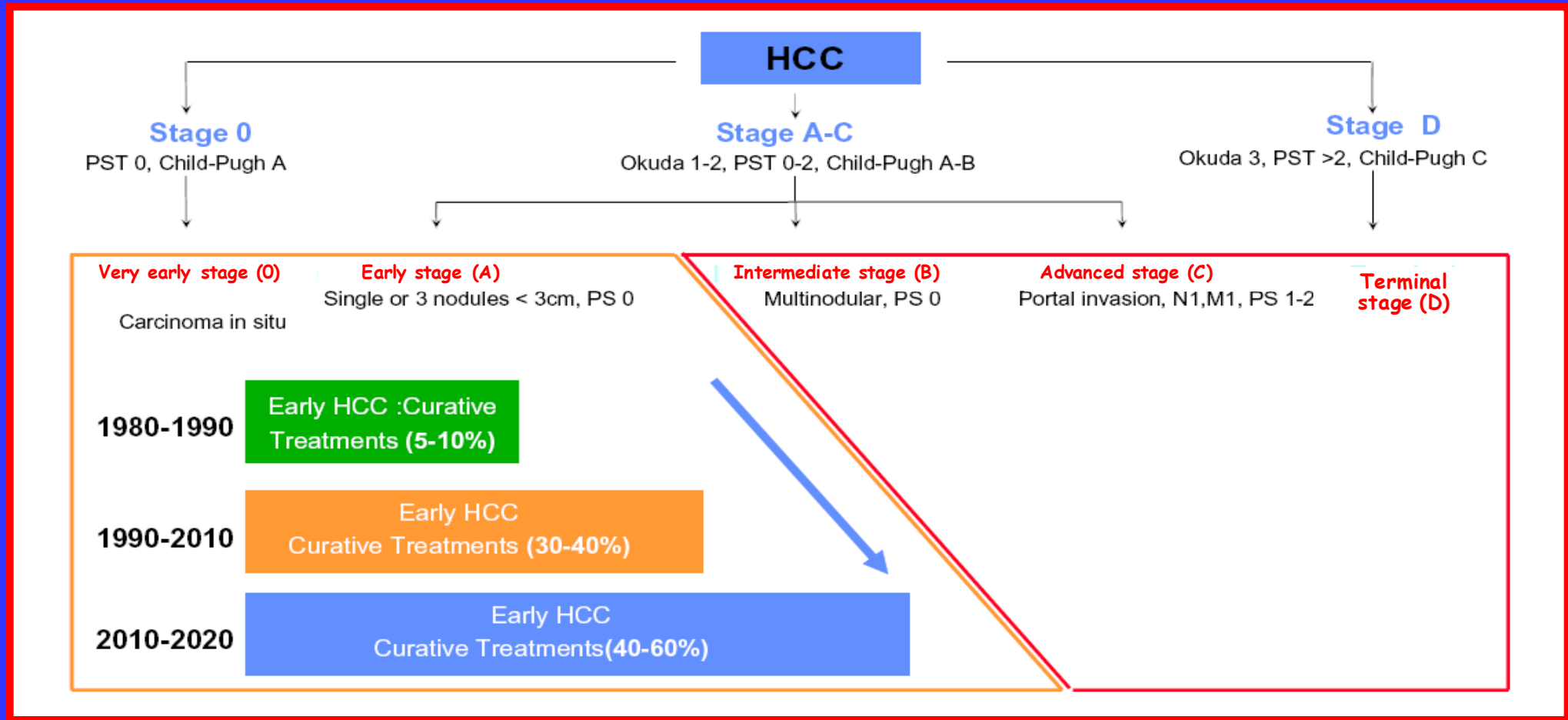


Number at risk	0	2	4	6	8	10	12
Non-cirrhosis	731	591	376	252	158	82	37
Cirrhosis	98	77	41	23	12	5	2

# I benefici della resezione epatica dell'HCC nei vari stadi BCLC



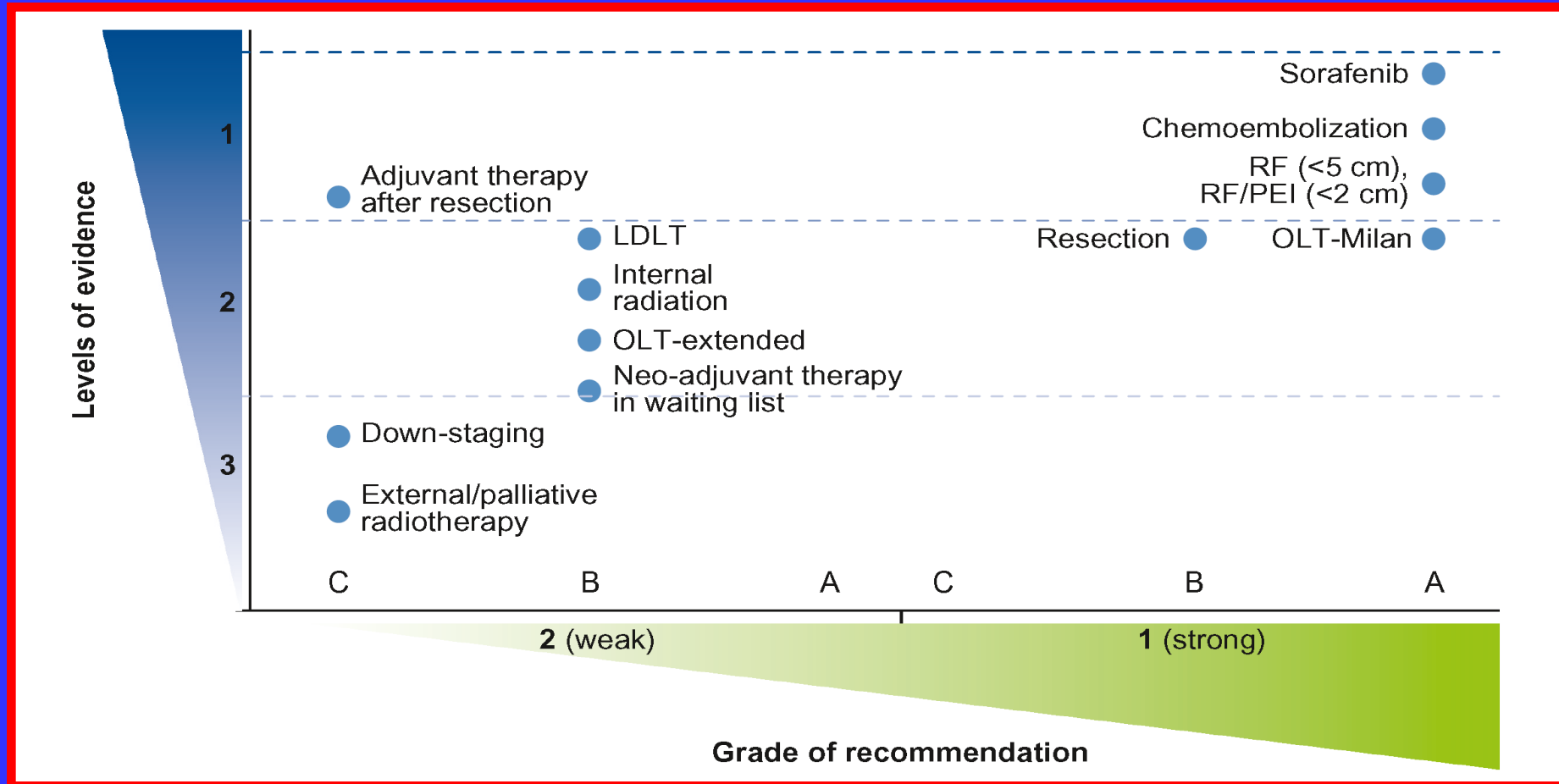
# Diagnosis of early HCC-curative treatments



Llovet JM et al J Hepatology 2008

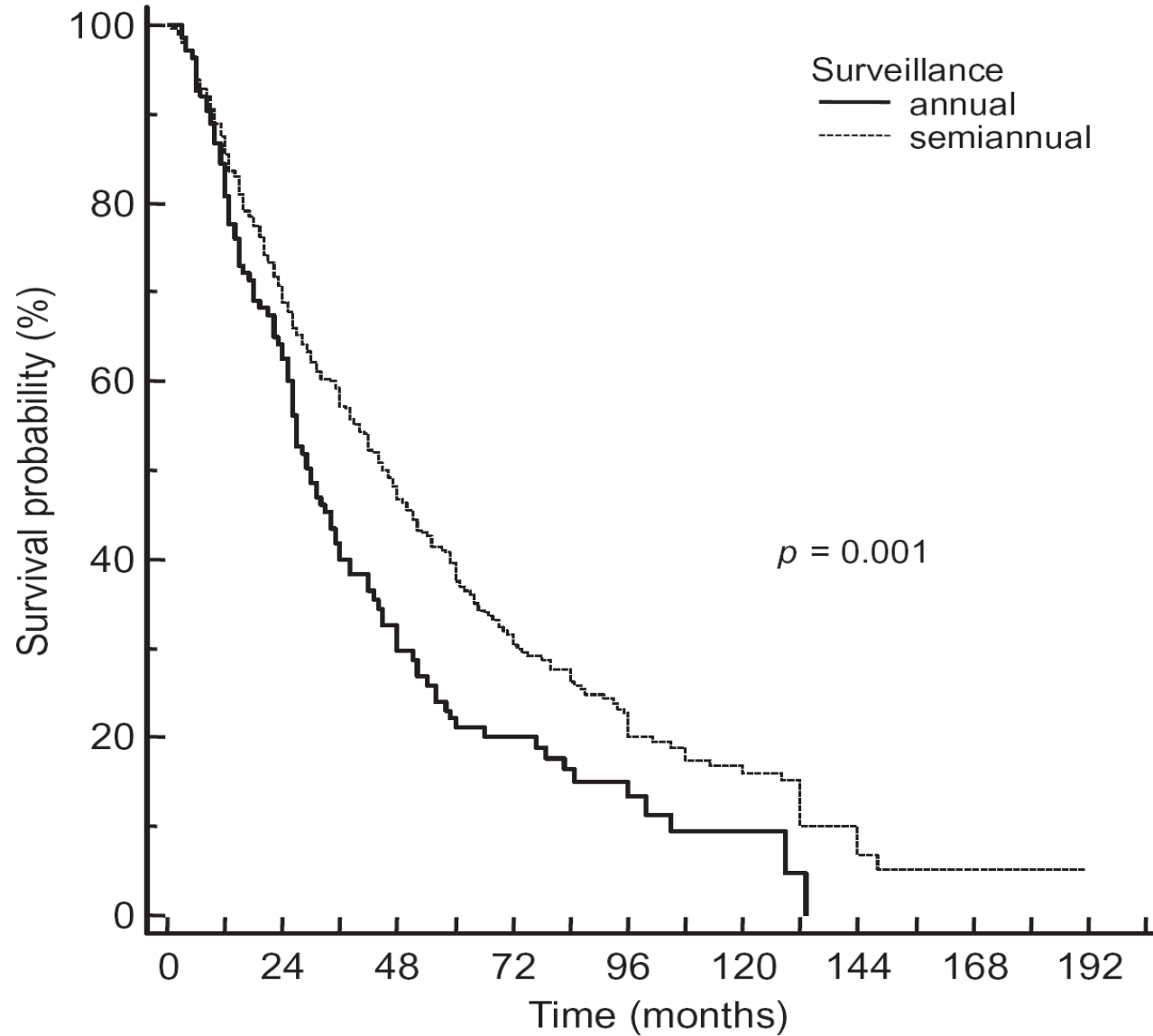


# Representation of EASL-EORTC recommendations



Journal of Hepatology 2012

Observed survival of patients under semiannual (510) or annual (139) surveillance



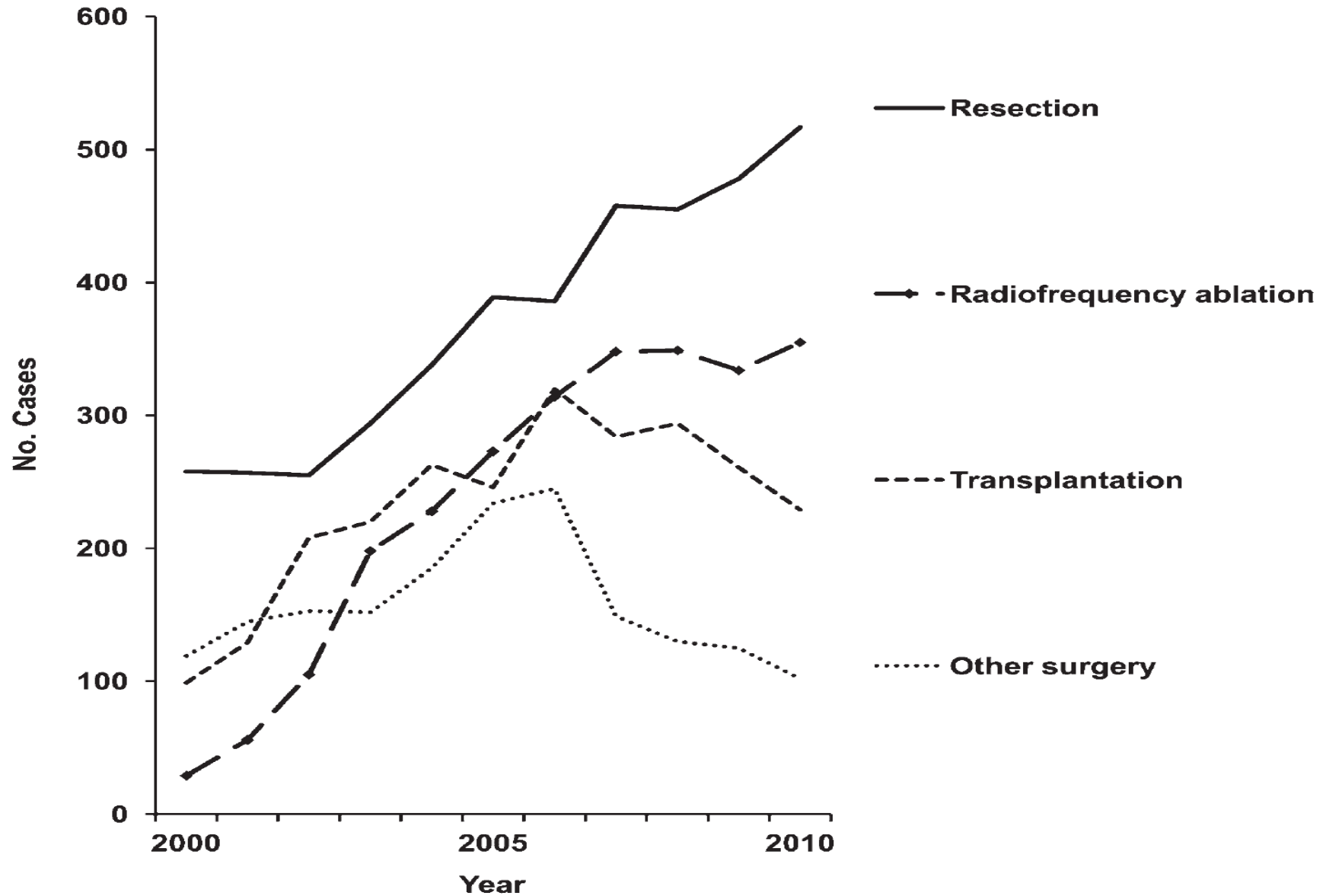
## Caratteristiche cliniche degli HCC sottoposti a trapianto epatico non-NASH vs HCC NASH-correlati

	Non-NASH HCC %	N	NASH HCC %	N	P Value
Male	79.2%	7,066	70.6%	807	<0.001
Age (mean $\pm$ SD)	57.2 $\pm$ 7.6		59.3 $\pm$ 7.3		<0.001
BMI (mean $\pm$ SD)	27.3 $\pm$ 4.9		33.6 $\pm$ 4.3		<0.001
Race/Ethnicity					<0.001
Non-Hispanic White	63.3%	5,582	75.3%	852	
Black	10.3%	907	6.4%	72	
Asian	12.5%	1,098	2.5%	28	
Hispanic	13.9%	1,227	15.9%	180	
MELD (mean $\pm$ SD)	13.7 $\pm$ 7.4		14.0 $\pm$ 7.3		0.11
Diabetes	20.8%	1,743	42.8%	450	<0.001
Cardiac Disease	3.2%	88	5.3%	13	0.08
Ascites	55.0%	4,900	59.1%	672	0.01
Encephalopathy	39.8%	3,541	41.5%	472	0.27

Comparisons are presented as proportion (%) and frequency (n) unless otherwise indicated.

NASH, nonalcoholic steatohepatitis; HCC, hepatocellular carcinoma; BMI, body mass index; MELD, model for endstage liver disease.

# Casi di HCC e trattamenti dal 2000 al 2010



# Association between family history of liver cancer and HCC risk

