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The Long Term Impact of Treatment on Outcome of Liver Disease

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G. B. 52 yr old, Manager

2009: Diagnosis of HCV+ Chronic Hepatitis

Medical History

IVDA 1977 for 12 months

No current alcohol consumption, Wine at lunch and dinner in the past

Appendectomy and Tonsillectomy during childhood

No active medications

December 2009 - First Admission

Bilirubin total (dir.)	0.5 (0.1) mg/dL
AST	105 UI/L
ALT	103 UI/L
ALP	146 IU/L
g-GT	95 IU/L
Albumin	3.6 g/dL
Hb	14 g/dl
Platelets	140.000/mm ³
HBsAg, anti-HIV	neg/neg
NOSA	neg
HCV-RNA, Genotype	165.932 IU/ml, 3a

December 2009 - First Admission

Physical Examination: Mild Hepatomegaly and splenomegaly

BMI: 24 (73 Kg x 1.75 m)

US: Mild Hepatomegaly, portal vein 13 mm, Spleen diameter 135 mm

Fibroscan: 15.7 KPa, IQR 1.9, SR 91%

EGDS: No Varices

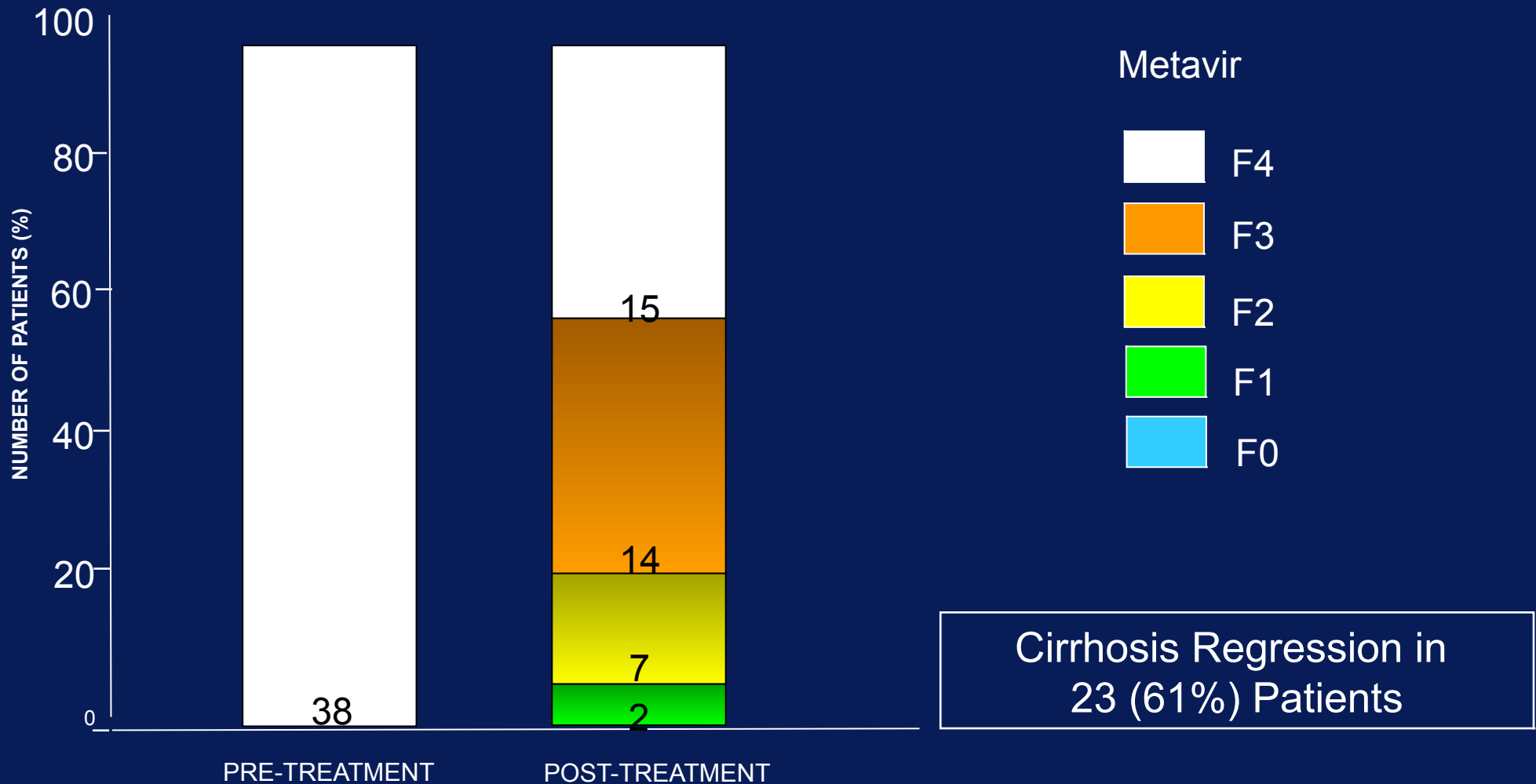
G. B. Summary in 2009

- 52 y.o. male
 - HCV-3 infection
 - Compensated cirrhosis
 - No significant co-morbidities
 - Naive to treatment
-

Systematic Review: Outcome of Compensated Cirrhosis Due to Chronic Hepatitis C Infection

Study	Sangiovanni <i>et al.</i>	Benvegna <i>et al.</i>	Hu and Tong	Serfaty <i>et al.</i>	Fattovich <i>et al.</i>	Toshikuni <i>et al.</i>	Degos <i>et al.</i>	Bruno <i>et al.</i>	Weighted mean
Death/ transplantation (%)	3.69	2.74	4.37	5.59	3.78	5.36	3.52	3.91	4.58
Liver failure	0.74	0.63	2.78	1.47	1.95	1.83			1.16
Varices	0.30	0.08		0.29		0.36			0.22
HCC	1.62	1.73	1.39	2.65	1.84	2.07			2.70
Nonliver	0.98	0.55	0.20	0.29	1.84	0.73			0.70
Complications (%)		4.04	4.76	7.65	7.79	11.70		2.77	6.37
HCC	3.34	2.69	1.79	3.24	2.49	5.60	2.54	2.33	3.36
Ascites	2.46	2.33	1.98			3.90			2.69
Variceal bleed	0.64	0.62	0.99			0.24			0.58
PSE	0.10	0.26	0.79			1.10			0.45
Jaundice	1.77		1.79			0.85			1.48

Rates of Cirrhosis Regression According to the METAVIR Scoring System



Cirrhosis Regression in HCV Patients Responding to Interferon-based Therapy

Study	Patients with cirrhosis (n)	Months from SVR	Staging System	Regression Rates
Reichard et al, 1999	3	24-96	Scheuer	3 (100%)
Arif et al, 2003	6	6-72	Ishak	5 (83%)
George et al, 2009	8	56	Ishak	6 (75%)
Poynard et al, 2002	37	<24	Metavir	25 (68%)
D'Ambrosio et al, 2012	38	48-104	Metavir	23 (61%)
Everson et al, 2008	40	6	Metavir	20 (50%)
Shiratori et al, 2000	24	12-120	Metavir	11 (46%)
Mallet et al, 2008	39	11	Metavir	17 (44%)
Pol et al, 2004	17	NA	Metavir	4 (24%)

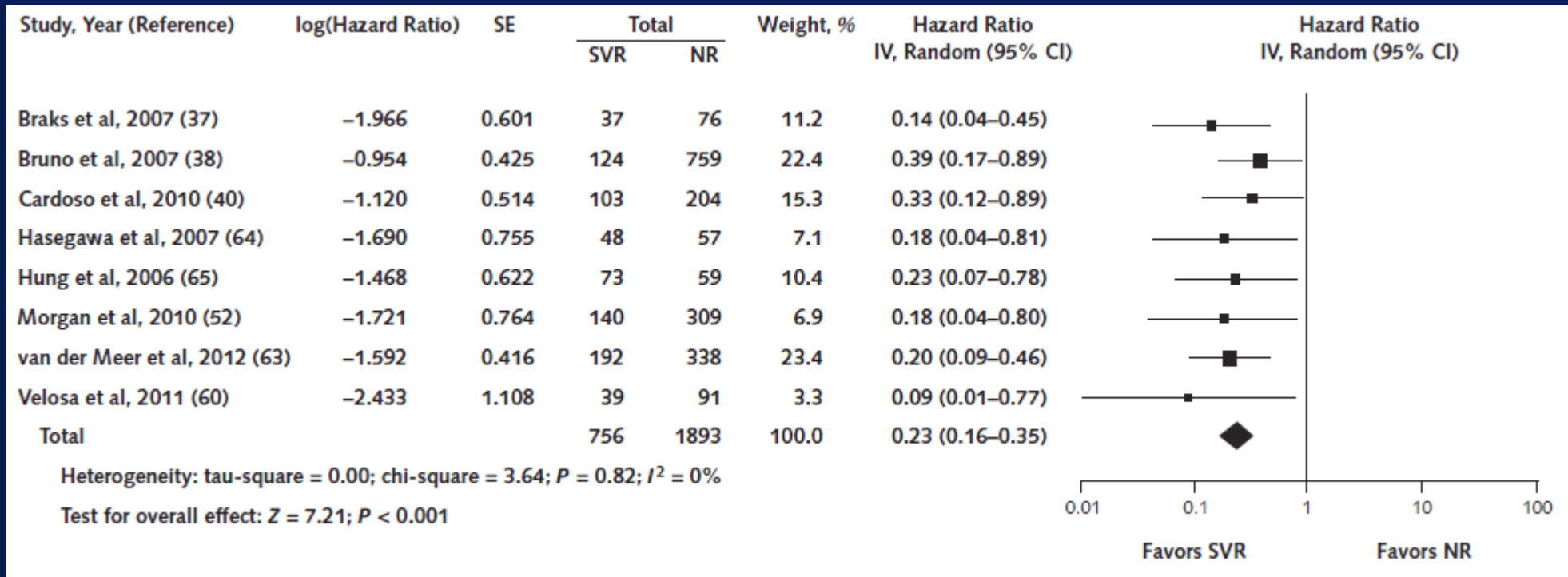
Why IFN Studies Are Unfit to Assess Chemoprevention of Viral Hepatitis Related HCC

1. Designed to assess antiviral efficacy of regimens by surrogate end-points.
 - ➔ *Underpowered to capture hard end-points of hepatitis including HCC*
 2. Enrolment skewed towards less severe hepatitis to improve compliance.
 - ➔ *Risk of HCC diluted*
 3. Different length/accuracy of f-up between SVR+ and SVR- patients.
 - ➔ *Selection bias*
 4. Lack of pretreatment patient stratification by HCC predictors
 - ➔ *Comparison between studies compromised*
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Eradication of HCV Infection and the Development of HCC

A Meta-analysis Of Observational Studies

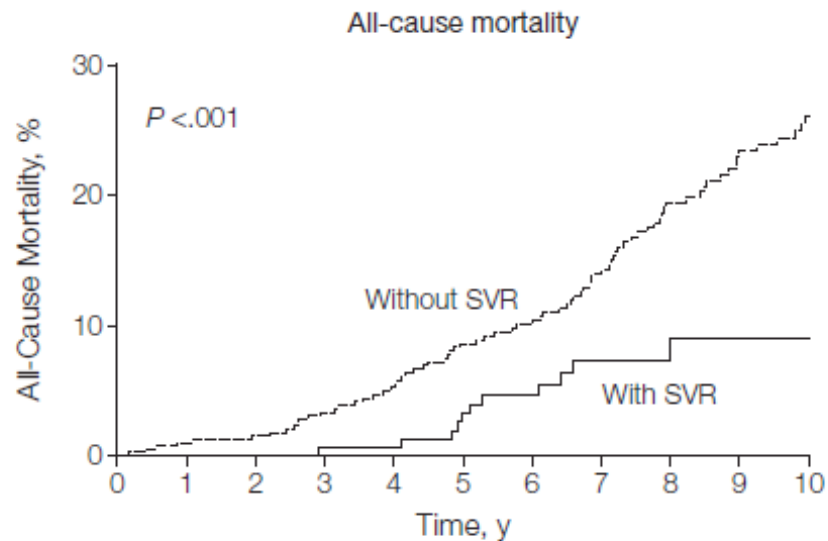
Persons With Advanced Liver Disease



SVR to IFN- α Is Associated with Improved Outcome in HCV Related Cirrhosis: A Retrospective Study in Italy

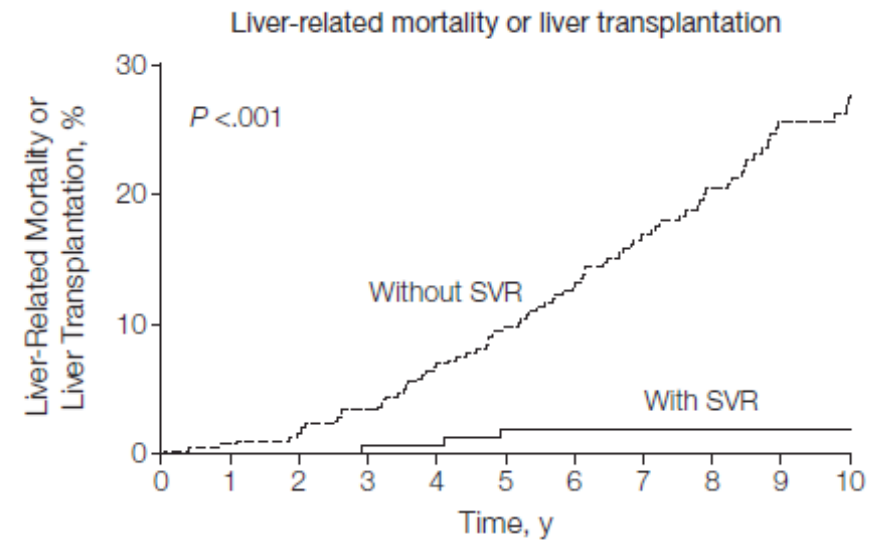
Strata	No. Patients	Person-yr	No. Event	Rate/100 Person-yr (95% CI)	Rate Ratio (95% CI)
Liver-related complications					
Non-SVR	759	5,703	107	1.88 (1.54-2.27)	n.a.
SVR	124	1,061	0	0 (0-0.35)	
HCC					
non-SVR	759	5,805	122	2.10 (1.75-2.51)	3.12 (1.42-6.86)
SVR	124	1,055	7	0.66 (0.27-1.87)	
Liver-related mortality					
non-SVR	728	5,781	83	1.44 (0.14-1.78)	7.59 (1.84-31.29)
SVR	120	1,019	2	0.19 (0.02-0.71)	
Non liver-related mortality					
non-SVR	759	6,004	31	0.52 (0.35-0.73)	1.28 (0.44-3.68)
SVR	124	1,077	4	0.37 (0.1-0.96)	

Survival Outcomes in Patients with Advanced Hepatic Fibrosis Due to HCV



No. at risk

Without SVR	405	393	382	363	344	317	295	250	207	164	135
With SVR	192	181	168	162	155	144	125	88	56	40	28



No. at risk

Without SVR	405	392	380	358	334	305	277	229	187	146	119
With SVR	192	181	168	162	155	144	125	88	56	40	28

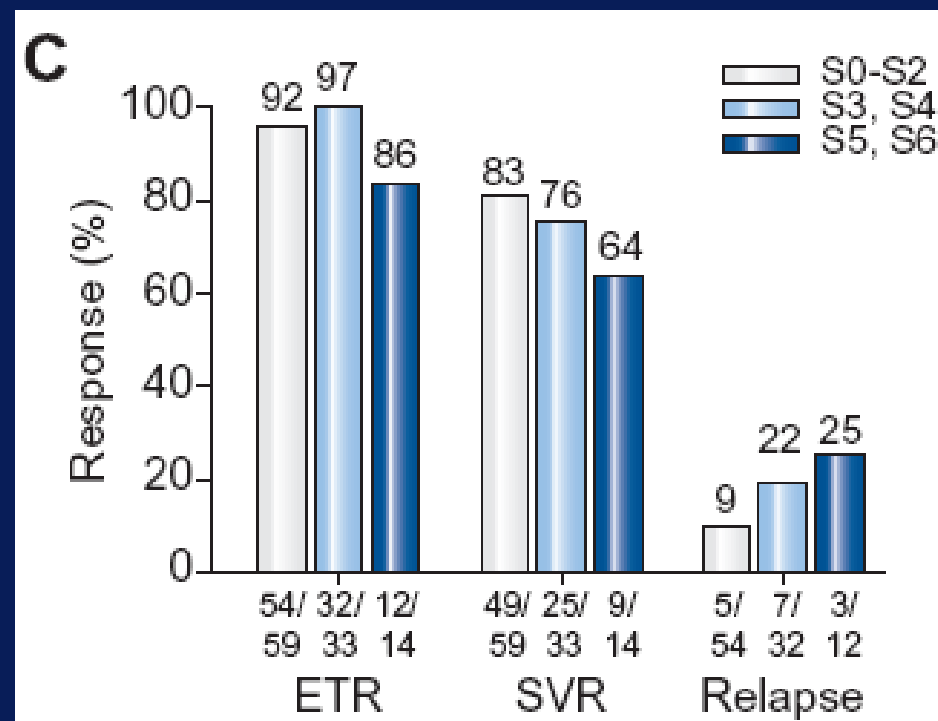
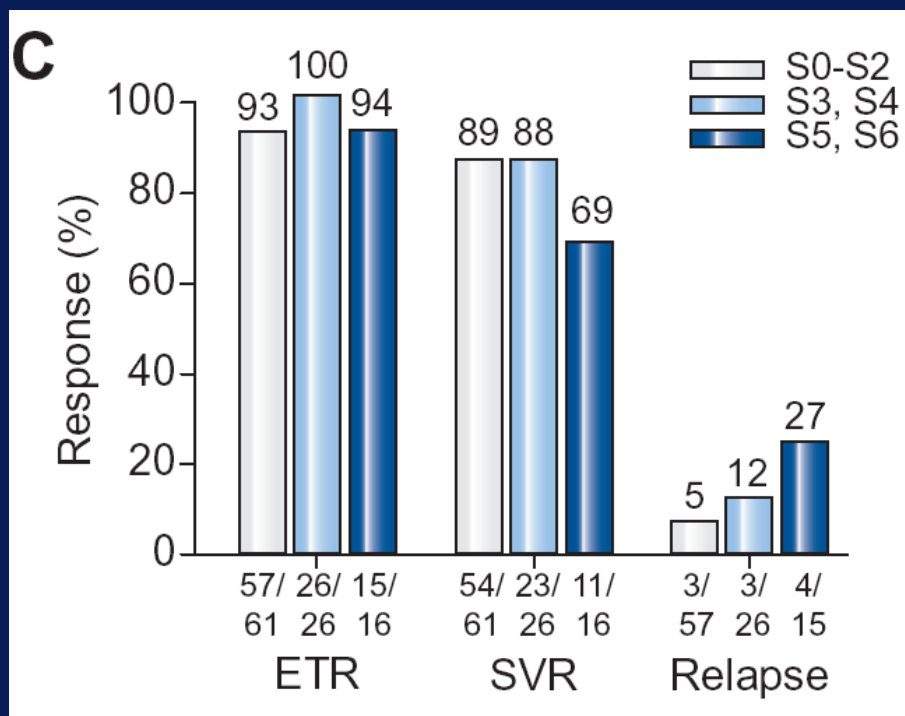
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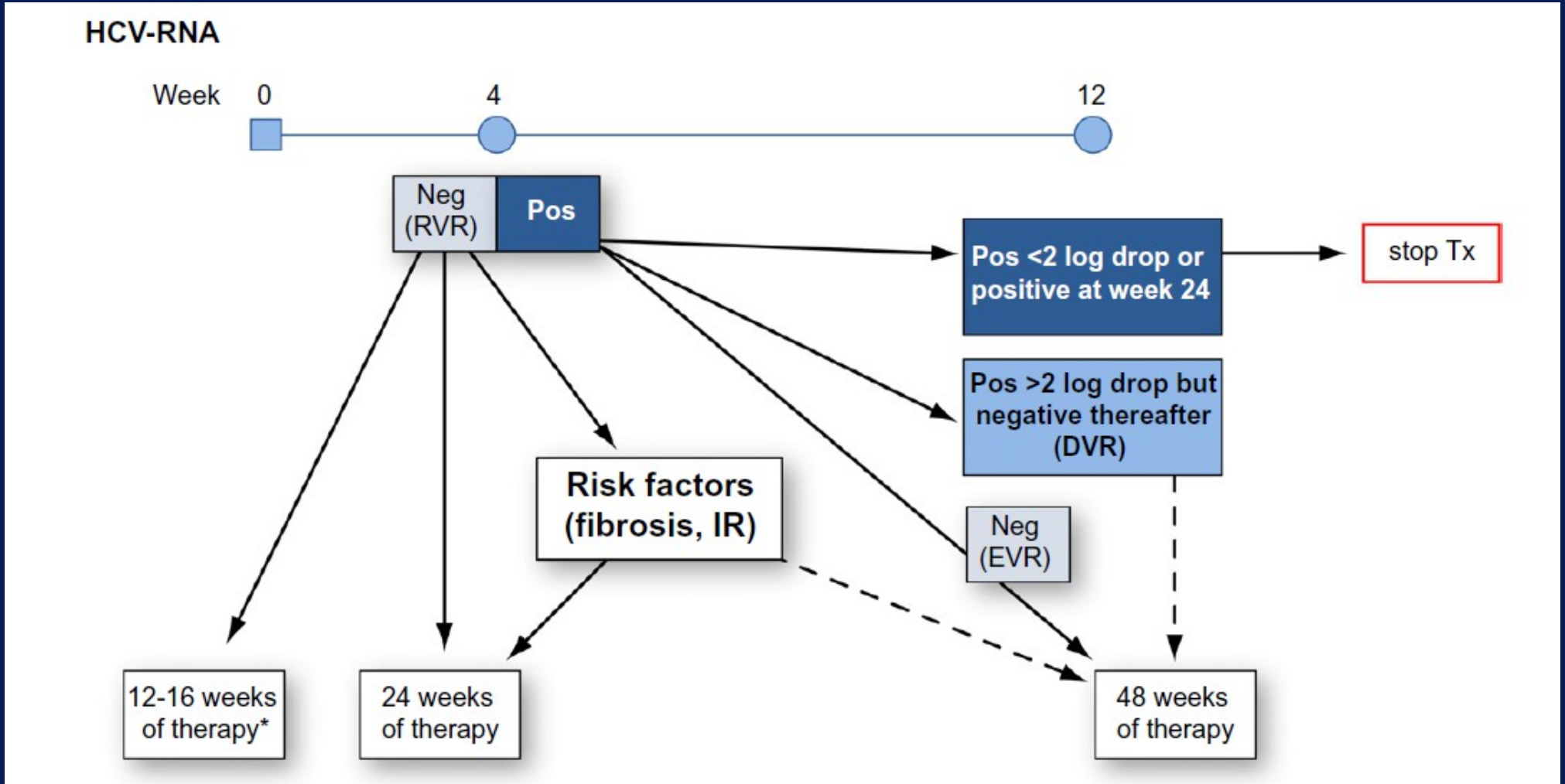
High Rates of Post-treatment Relapse in HCV-2 and 3 Patients with Advanced Fibrosis

PegIFNalpha2a + Rbv 800 mg

PegIFNalpha2b + Rbv 800-1200 mg



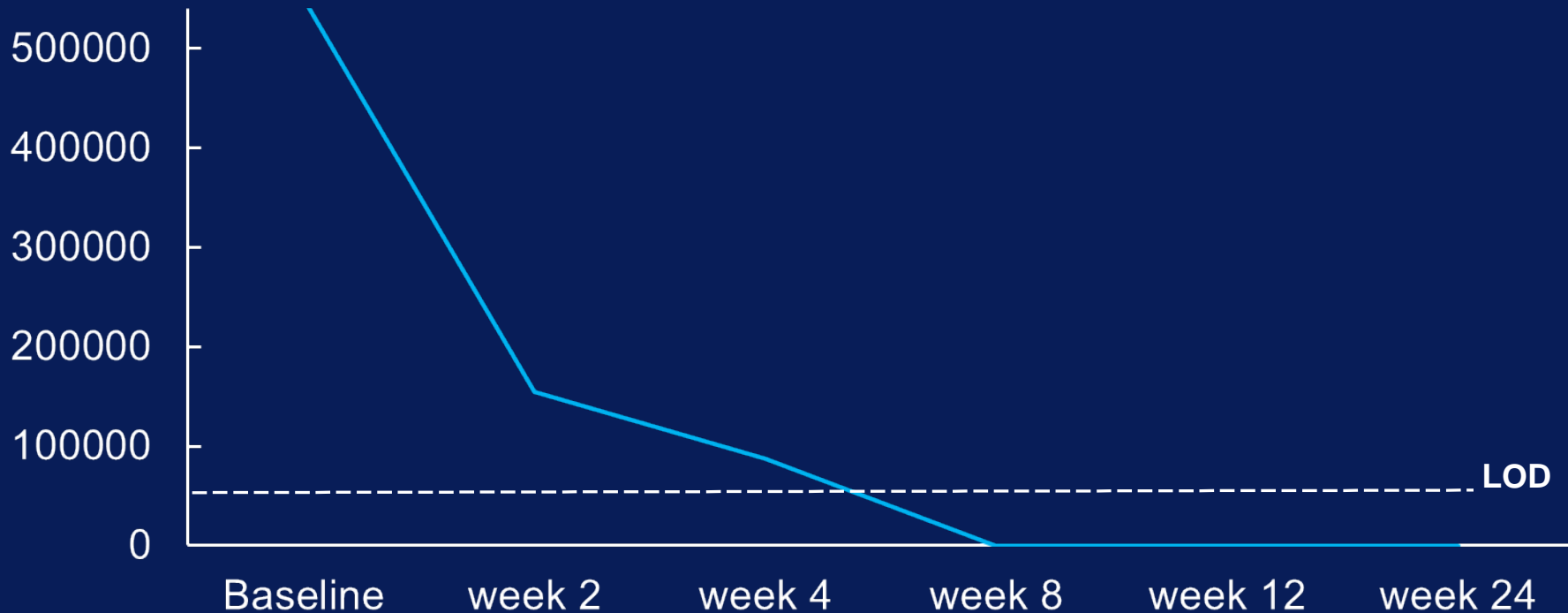
Response Guided Treatment Duration in HCV-3 Patients: The EASL Clinical Practice Guidelines



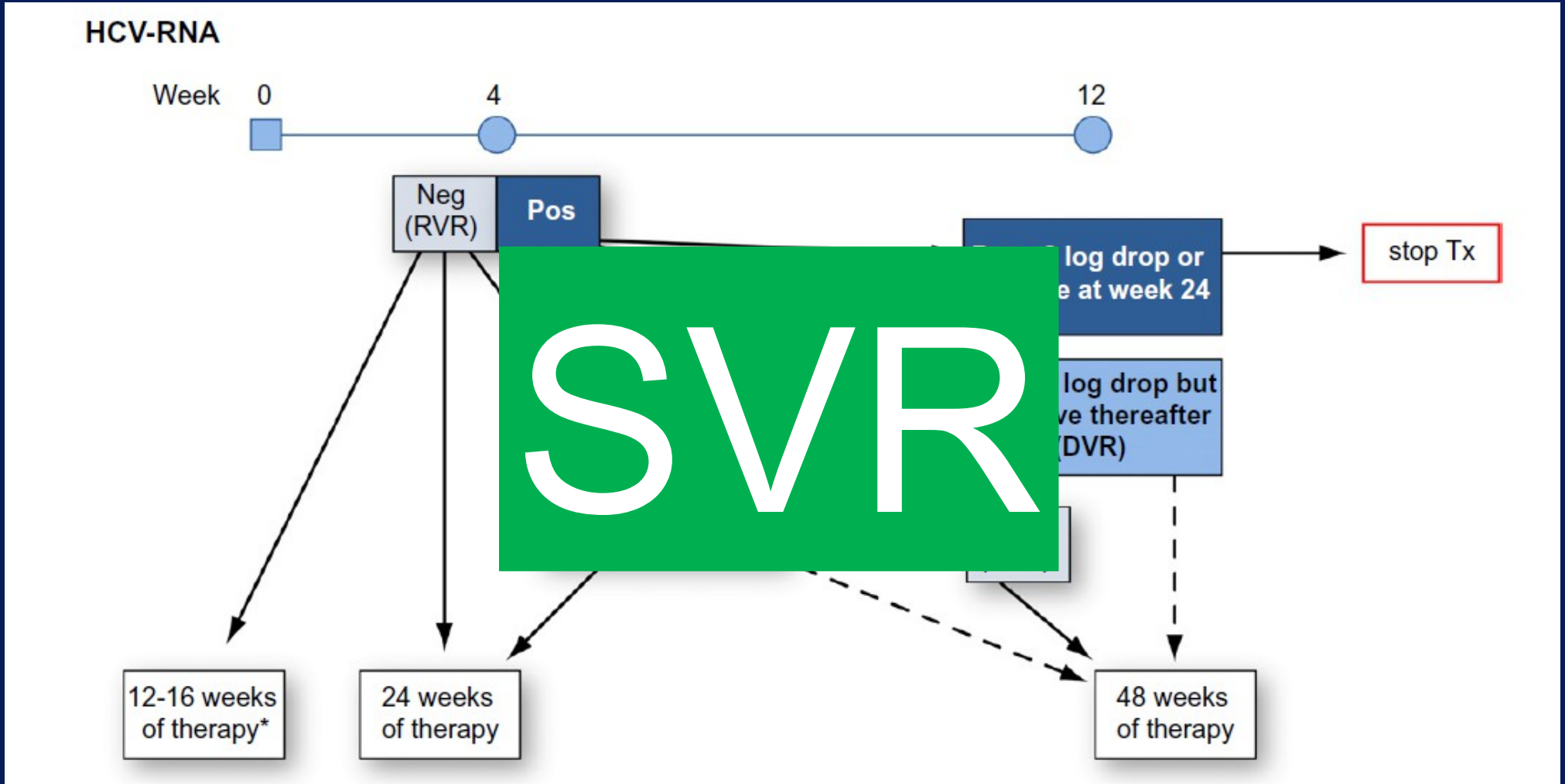
G. B. 52 yr old, Manager

PegIFNalpha2a 180mcg/wk + Ribavirin 800 mg/day (29/12/2009)

HCV RNA



Response Guided Treatment Duration in HCV-3 Patients: The EASL Clinical Practice Guidelines



G. B. Summary in 2010

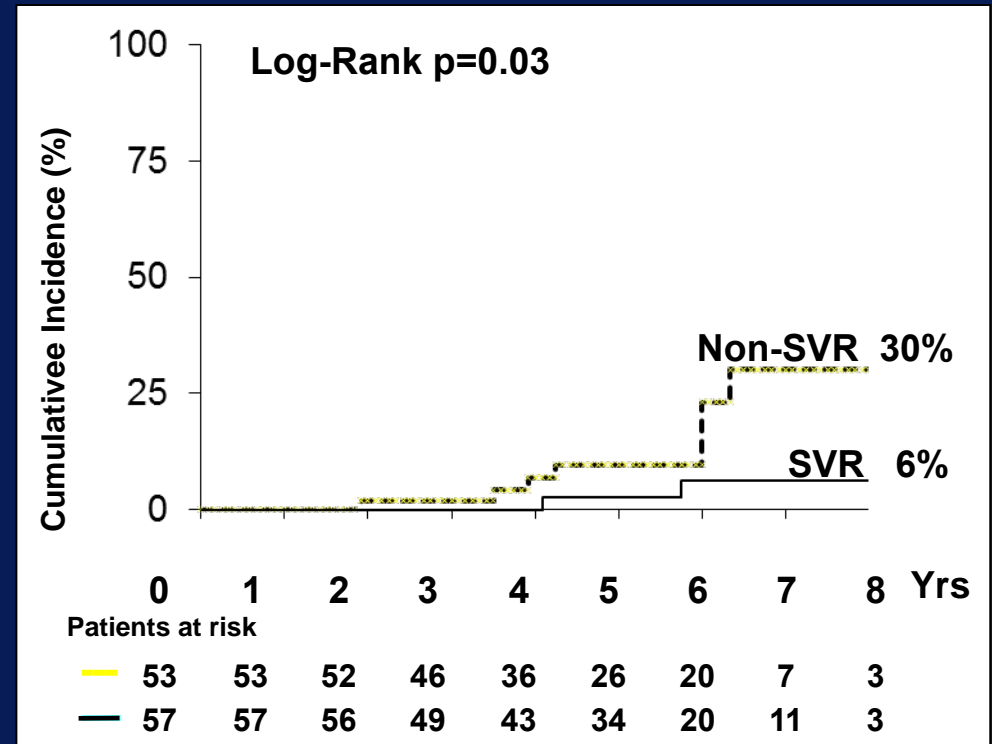
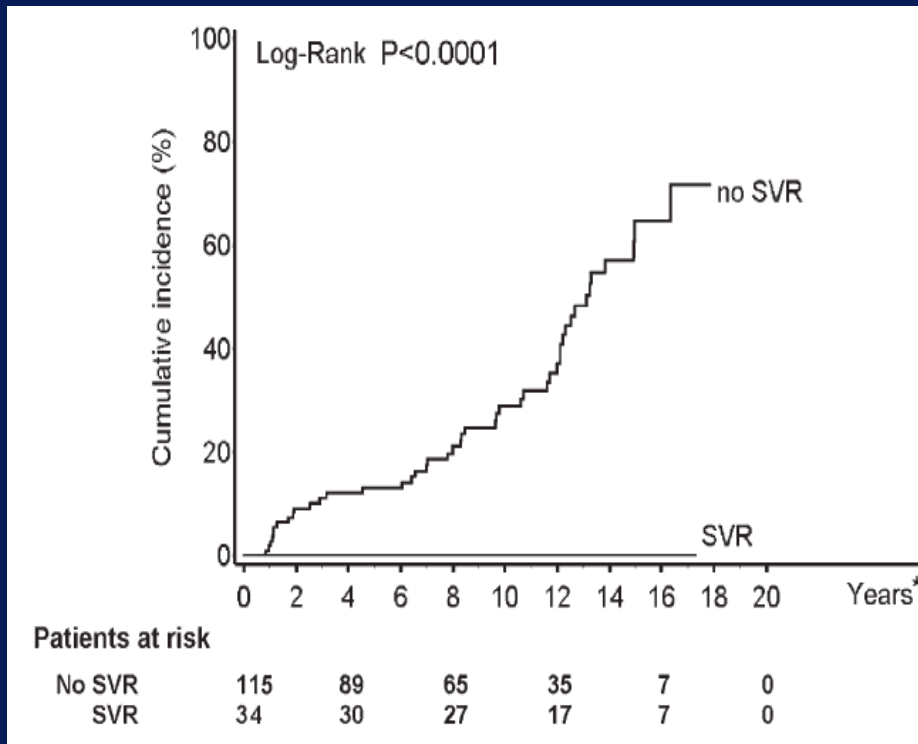
- 53 y.o. male
- Compensated cirrhosis with an SVR
- No significant co-morbidities

How should we follow the patient?

Cumulative Incidence of Clinical Events in HCV Patients with Cirrhosis Stratified by Treatment Response

Endpoint	Patients	SVR (+)	SVR (-)	Reference	
Hepatocellular Carcinoma	271	17.0%	35.0%	Shiratori	2005
	307	5.8%	19.6%	Cardoso	2010
	920	5.6%	16.0%	Bruno	2007
	2890	1.9%	17.9%	Yoshida	1999
Clinical Decompensation	307	2.9%	13.7%	Cardoso	2010
	479	0%	12.0%	Veldt	2007
Development of Esophageal Varices	127	3.5%	15.1%	D'Ambrosio	2011
	218	0%	39.0%	Bruno	2010
Liver-related Death	307	2.9%	8.8%	Cardoso	2010
	920	1.7%	11.4%	Bruno	2007
	2879	0.2%	2.0%	Yoshida	2002
	271	0%	15.0%	Shiratori	2005

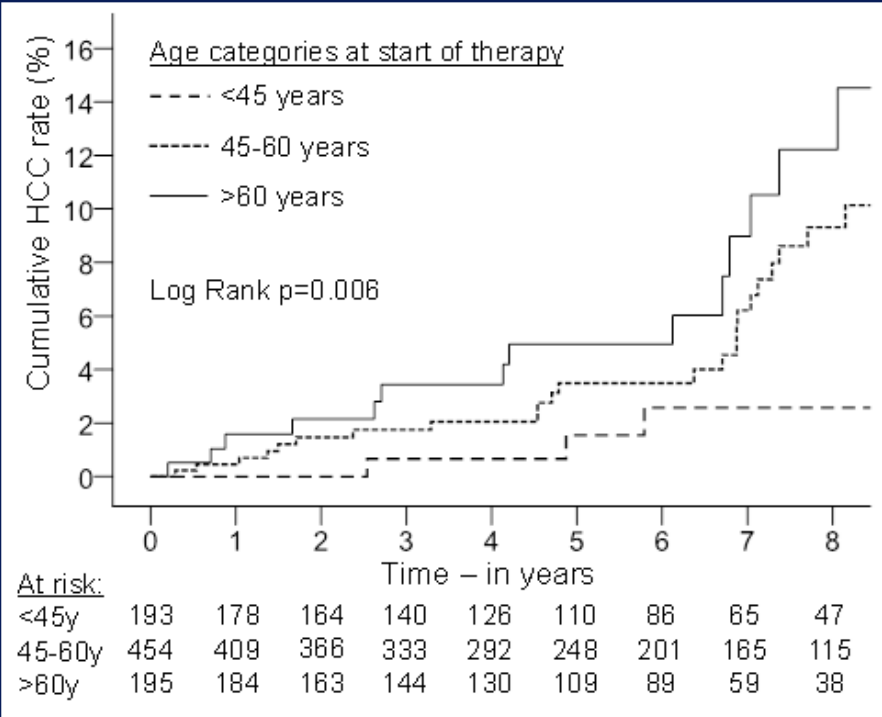
The Impact of an SVR on Development of Esophageal Varices in HCV Cirrhotics



The Risk of HCC Among Patients with Cirrhosis Following Sustained Virological Response

The study

- 10 Liver Centers in EU and Canada
- 1001 patients, 843 F4, 158 F2/F3
- 50 patients developed HCC during 5.7 yr f-up
- Cumulative 8 yr HCC rate: F4=8.5%
F3=1.8%

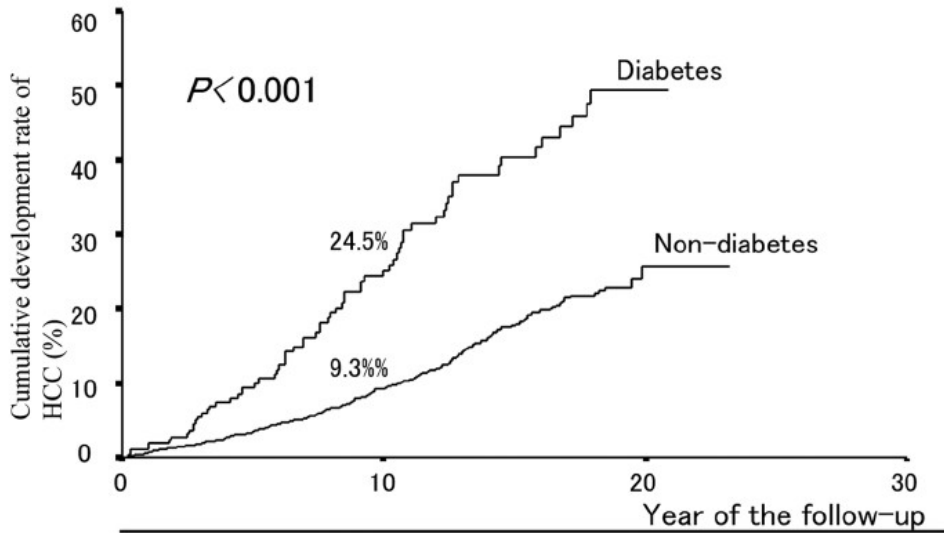


Effect Of Aging On Risk For Hepatocellular Carcinoma In Chronic Hepatitis C Virus Infection

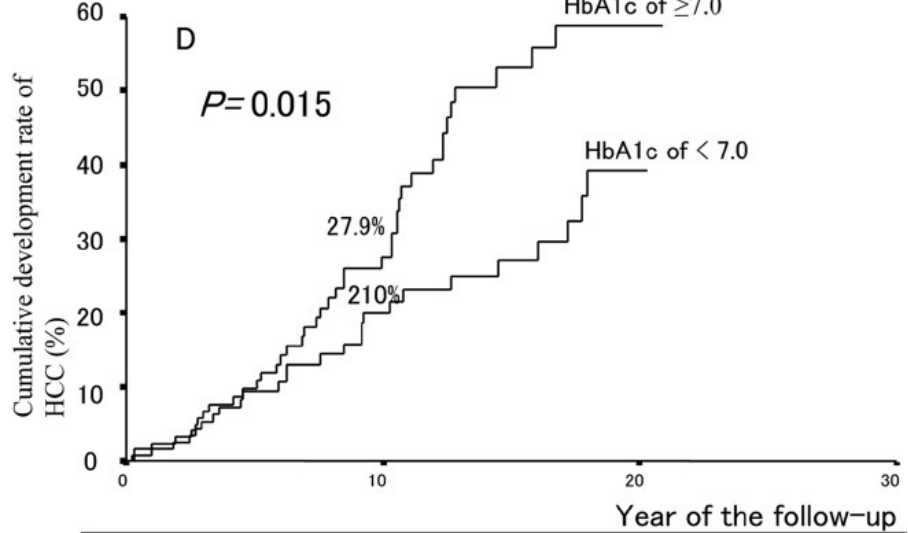
Annual incidence of HCC after IFN

Group	Total, %	< 65 years, %	≥ 65 years, %
F0/F1	0.2	0.1	0.9
F2	0.8	0.6	1.7
F3	2.5	1.8	4.6
F4	4.6	4.4	5.1
Total	1.1	0.8	2.4
SVR	0.4	0.2	1.3
Non-SVR	1.4	1.0	2.9

Effect of Type 2 Diabetes on Risk for Malignancies Includes Hepatocellular Carcinoma in Chronic Hepatitis C



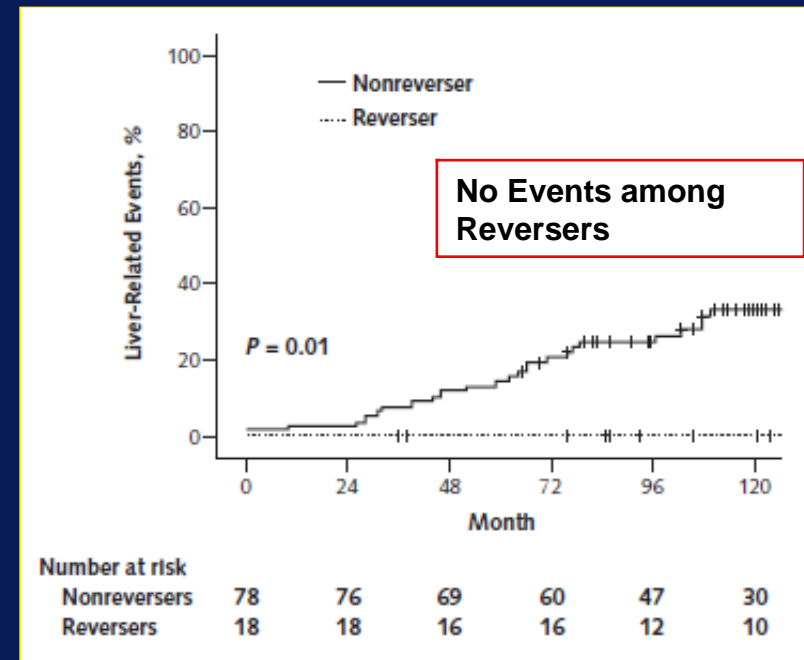
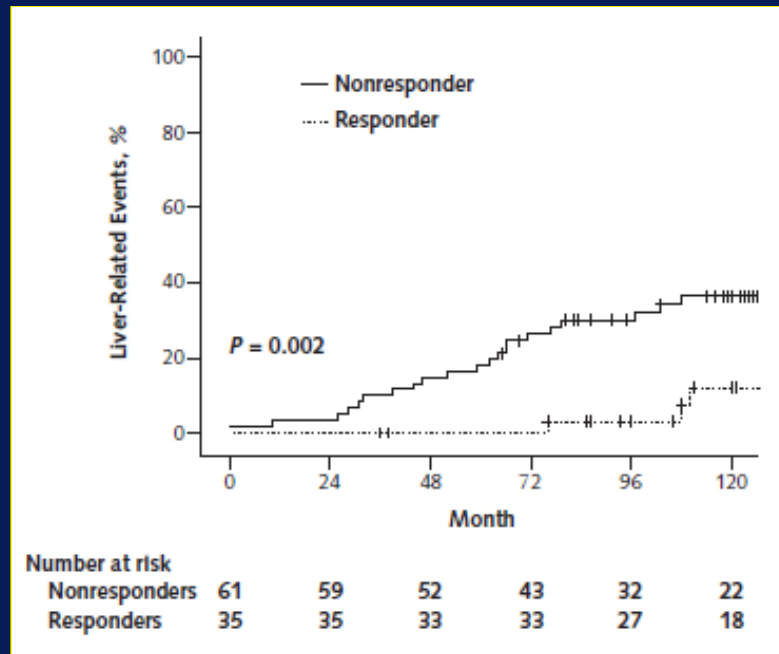
Glucose state	0y	5y	10y	15y	20y
Diabetes	267	172	102	49	2
Non-diabetes	4035	2593	1474	553	43



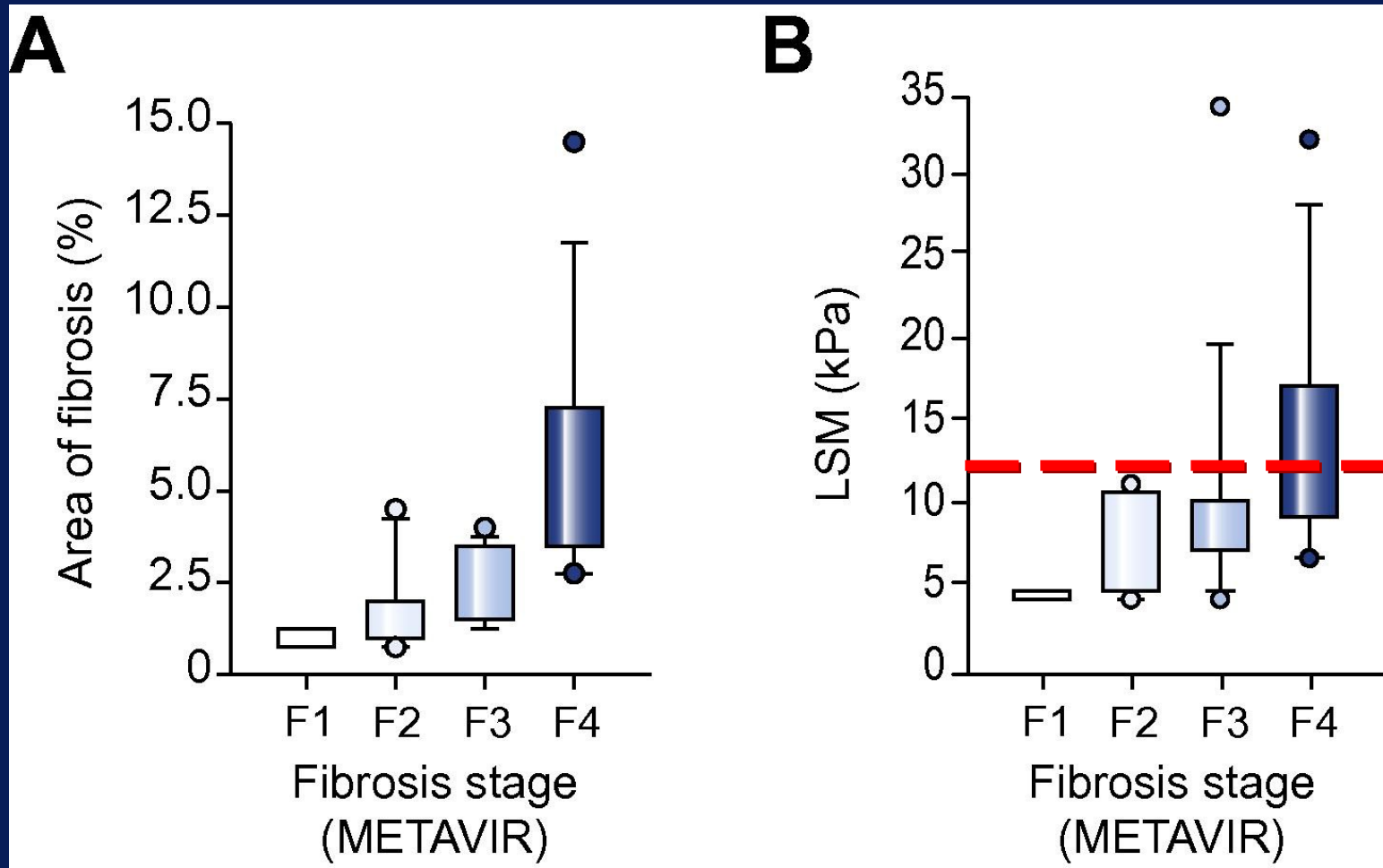
HbA1c (%)	0y	5y	10y	15y	20y
≥ 7.0	140	90	48	18	1
< 7.0	127	82	54	31	1

The Impact of Cirrhosis Regression on Clinical Events

Liver biopsy 11 months after SVR: cirrhosis regression in 17/39 (44%)



Transient Elastography Fails to Identify Cirrhosis Regression



A Novel Predictive Score For HCC Development In Patients With HCV After SVR To PegIFN and Ribavirin

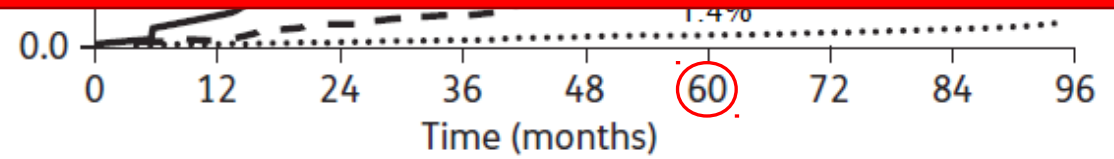
HCC Score



Surveillance with US every 6 months of all Cirrhotics with an SVR is Recommended

EASL & AASLD Guidelines

Auoc = 84.8%



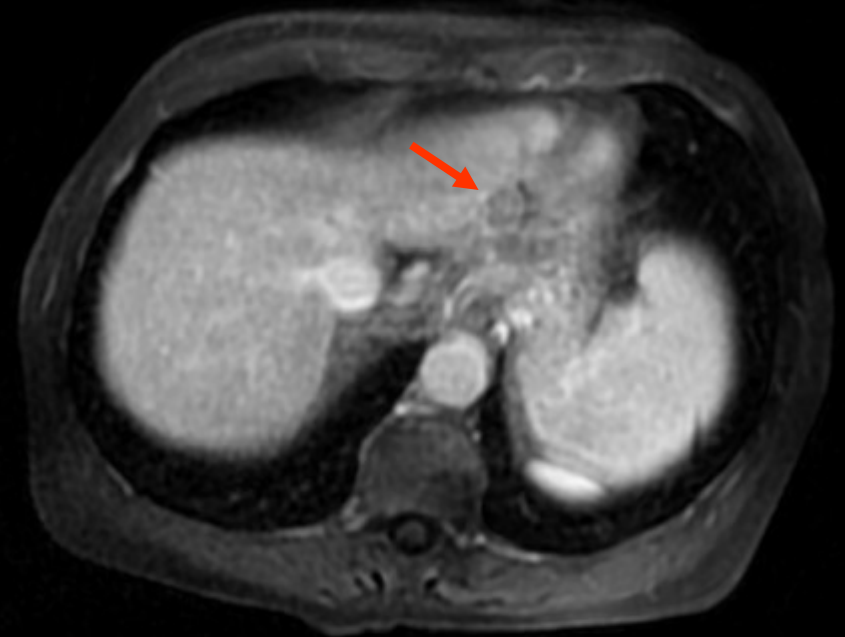
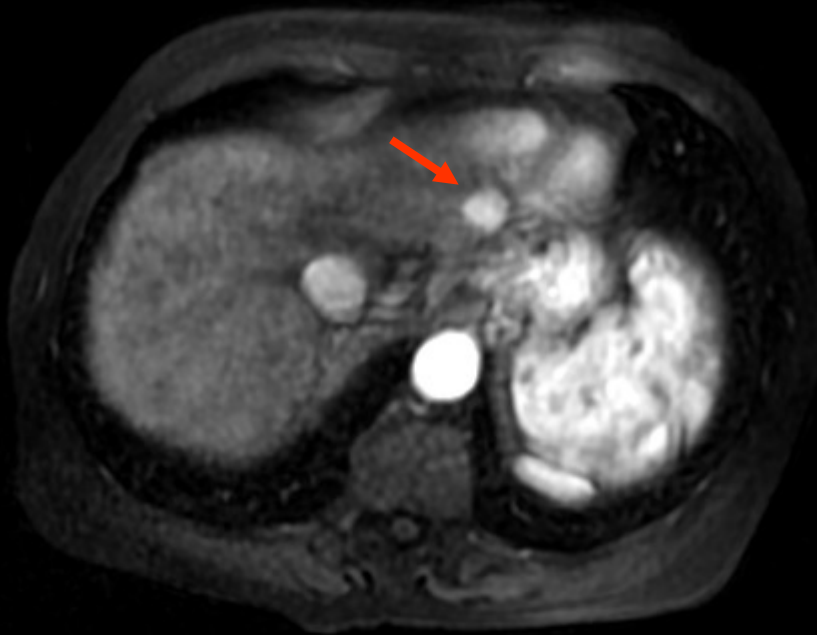
Follow-up

<u>Liver Function</u>	<u>Dec 2010</u>		<u>June 2011</u>		<u>Dec 2011</u>
• ALT IU/L	21	→	13	→	18
• HCV-RNA 10 ⁵ /IU/mL	ND	→	ND	→	ND
• Total Bilirubin mg/dL	1.2	→	1.2	→	1.2
• Albumin g/dL	3.6	→	3.7	→	4.0
• Prothrombin ratio	1.24	→	1.11	→	1.06
• Platelets 10 ³ /mmc	82	→	165	→	174
• AFP ng/mL	7	→	4	→	4
• Child-Pugh	A5	→	A5	→	A5
• Abdominal US	negative	→	negative	→	2 cm nodule in S2

First Evaluation at Our Center MRI December 2011

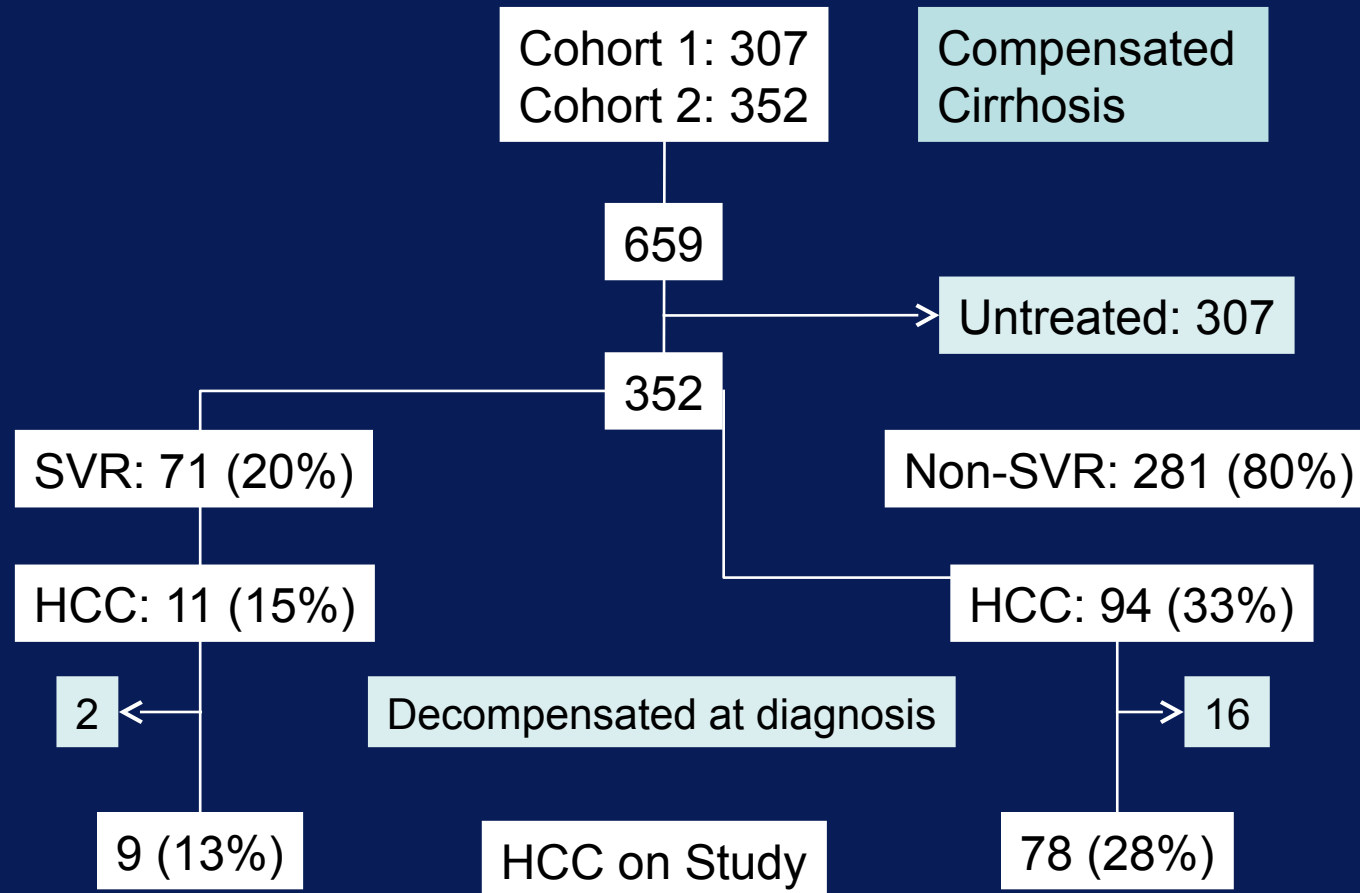
Wash-in

Wash-out



21 mm HCC nodule in S2

SVR to IFN Is Associated with Improved Survival in Hepatitis C Patients With a HCC

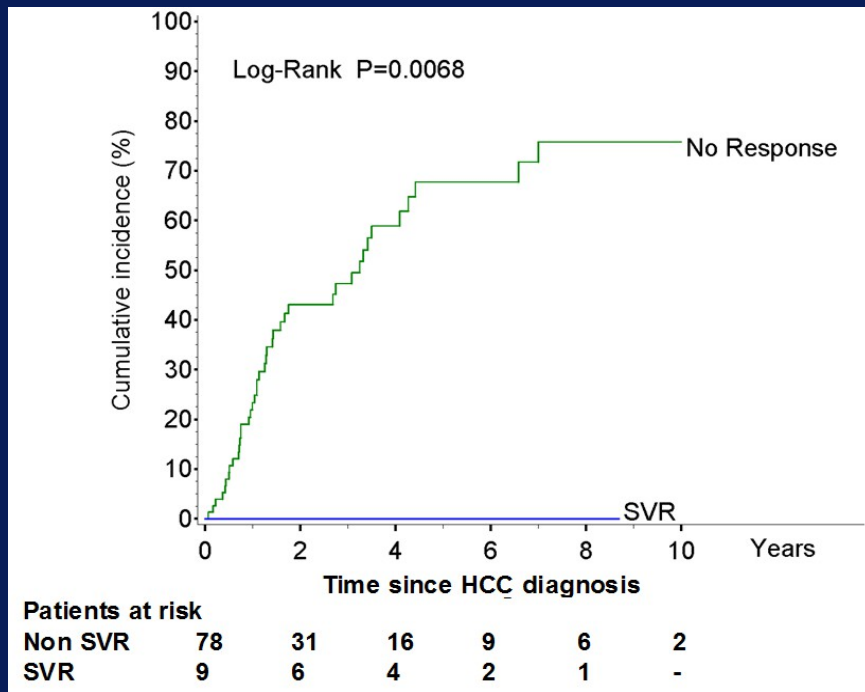


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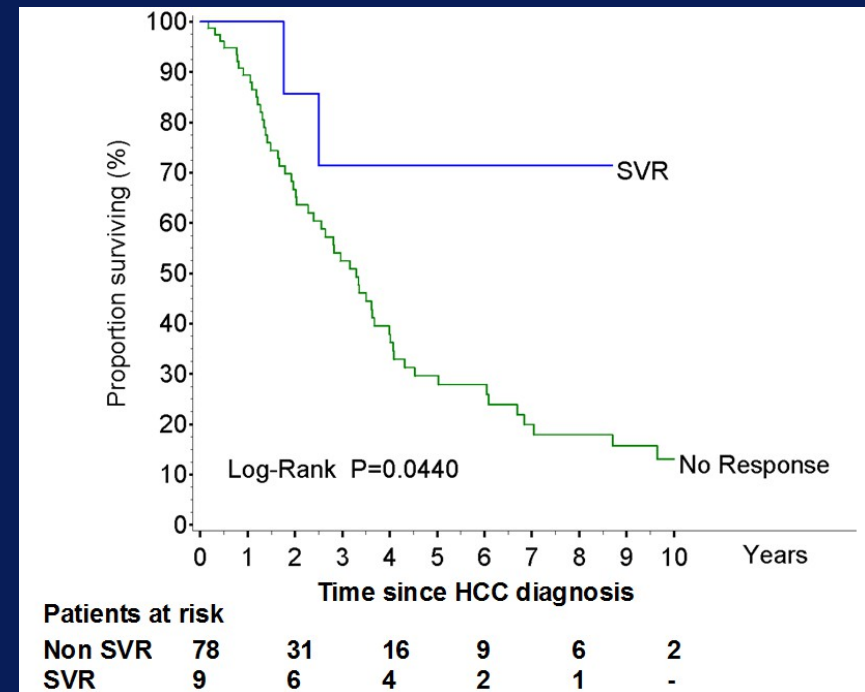
	SVR		Non-SVR		P-value
Patients, N	9		78		
Study time, mo. (range)	44	(7-104)	28	(1-214)	0.31
Males, N	8	(89%)	55	(71%)	0.43
Age, yr (range)	65	(46-79)	65	(46-82)	0.69
Single HCC, N	8	(89%)	58	(74%)	0.68
Liver decompensation, N	0	(0%)	43	(55%)	0.007
Deaths, N	2	(22%)	58	(74%)	0.04
Yearly mortality rates	5%		21%		

SVR to IFN Is Associated with Improved Survival in Hepatitis C Patients With a HCC

Liver related decompensation following HCC



Mortality following HCC development



SVR: a Gamebreaker for HCV Patients

Improvements in non cirrhotic patients

- Progression to cirrhosis
- Incidence of extra-hepatic manifestations (NHL, diabetes)
- Neuro-cognitive functions
- Health Related QOL
- Overall survival

Improvements in cirrhotic patients

- Clinical decompensation and variceal bleeding
- HCC incidence
- Cirrhosis regression
- Liver related survival