X Workshop Nazionale
Innovazione e Ricerca per la Pratica Clinica
TERAPIE INNOVATIVE
DELLE EPATITI CRONICHE VIRALI
Firenze, 13-14 gennaio 2020
Centro Congressi Hotel Londra

Follow-up del paziente a rischio di sviluppo di HCC

Piero Colombatto

UO Epatologia - *PISA*

Centro di Riferimento regione Toscana per "la Diagnosi e il Trattamento delle Epatopatie Croniche e del Tumore di Fegato"

The Evolution of HCV Care and Treatment Implementation

Pan-genotypic, high genetic barrier and antiviral activity

Short

Shorter durations of therapy (up to 8 weeks!!)

Simple

No need for Ribavirn

Minimal on-treatment monitoring

Effective

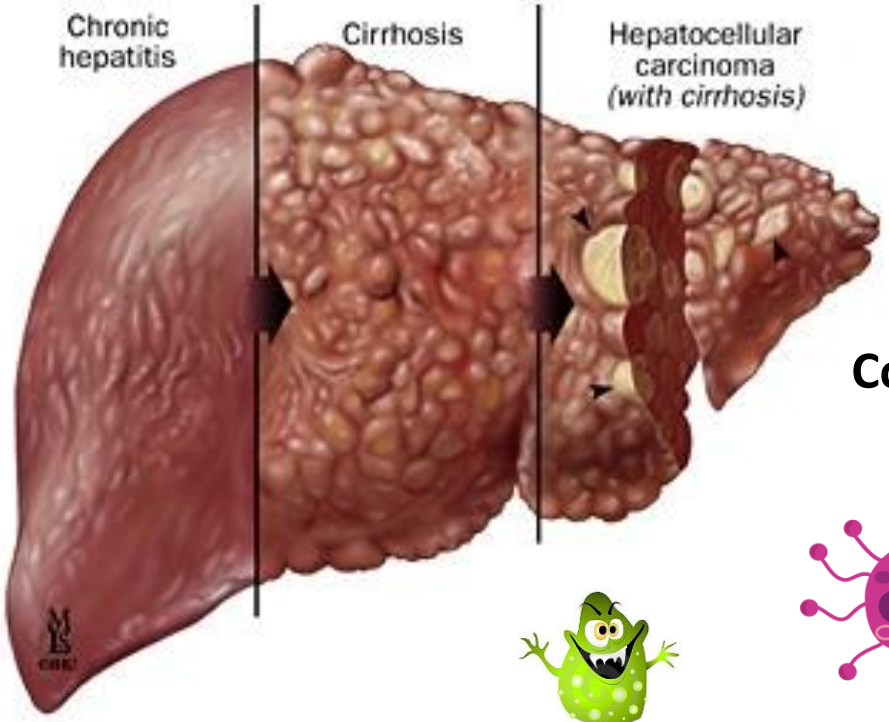
Consistently high overall SVR rate in most patient populations

Safe

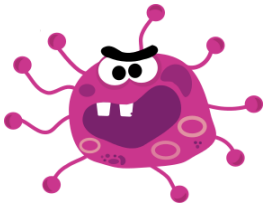
Consistently low rate of adverse safety events and drug to drug interecations

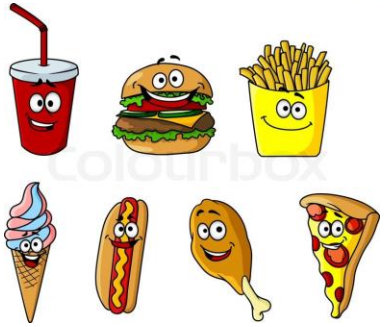
DAAs treatment and liver

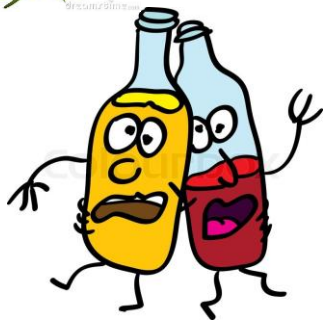
Stage of liver disease at the time of treatment



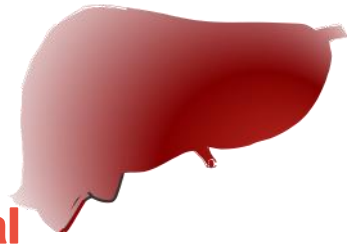
Co-factors of liver damage



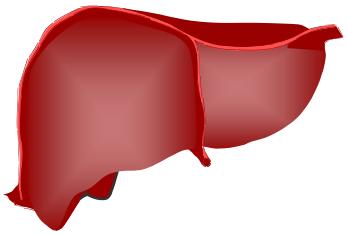




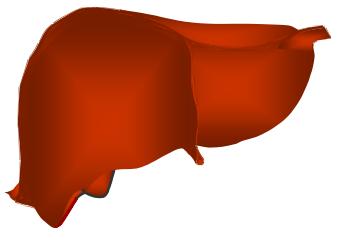
Natural history of chronic hepatits C



Normal Liver



Chronic hepatitis



Cirrhosis

Cirrhosis complications

Liver failure
Bleeding
HCC

10 to 40 years in a non-linear fashion

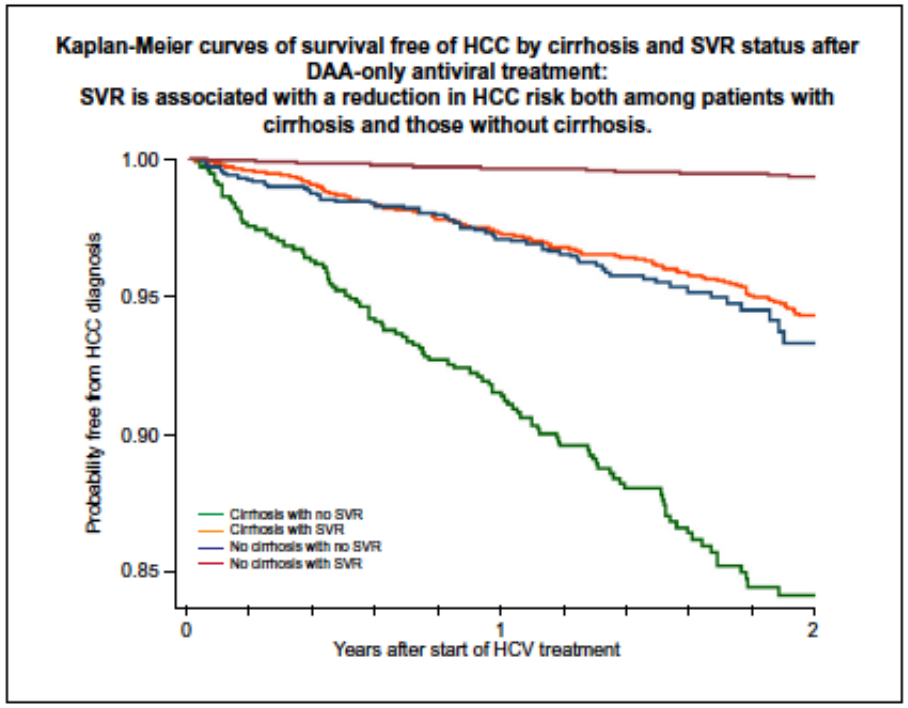
DAAs Therapy

Slows progression, reduces, but not abolishes complications

Progression in about 30% of cases

HCV eradication induced by DAAs reduces the risk of HCC

- 62354 pts treated in the Veteran Affairs national Health Care System from 1999 to 2015 [IFN only 58%; DAA+IFN (7.2%); DAA35%) and were followe-up until 15 June 2017
- Incident cases of HCC → diagnosis at least 180 days after DAA start during a mean follow-up of 6.1 years



- 3271 incident cases of HCC, with lower incidence for SVR pts (0.43x100 pt/y vs 1.14)
- Overall **SVR** was associated with a **61% reduction** in **HCC risk**: IFN only AHR 0.32, DAA+IFN AHR 0.48; DAA AHR 0.29
- Analysis limited to 2 years f.u.: IFN AHR 0.56, DAA+IFN AHR 0.48; DAA AHR 0.28
- **HCC incidence** was **higher** in **DAA** treated pts (1.32x100 pt/y) vs DAA+IFN and IFN (1.06 & 0.81 x100 pt/y), but

there was **no significant association** between **HCC risk** and **treatment** after **adjusting** for **major confounding**

Ioannou GN et al , J Hep 2018

Post-treatment follow-up: Patients with advanced fibrosis

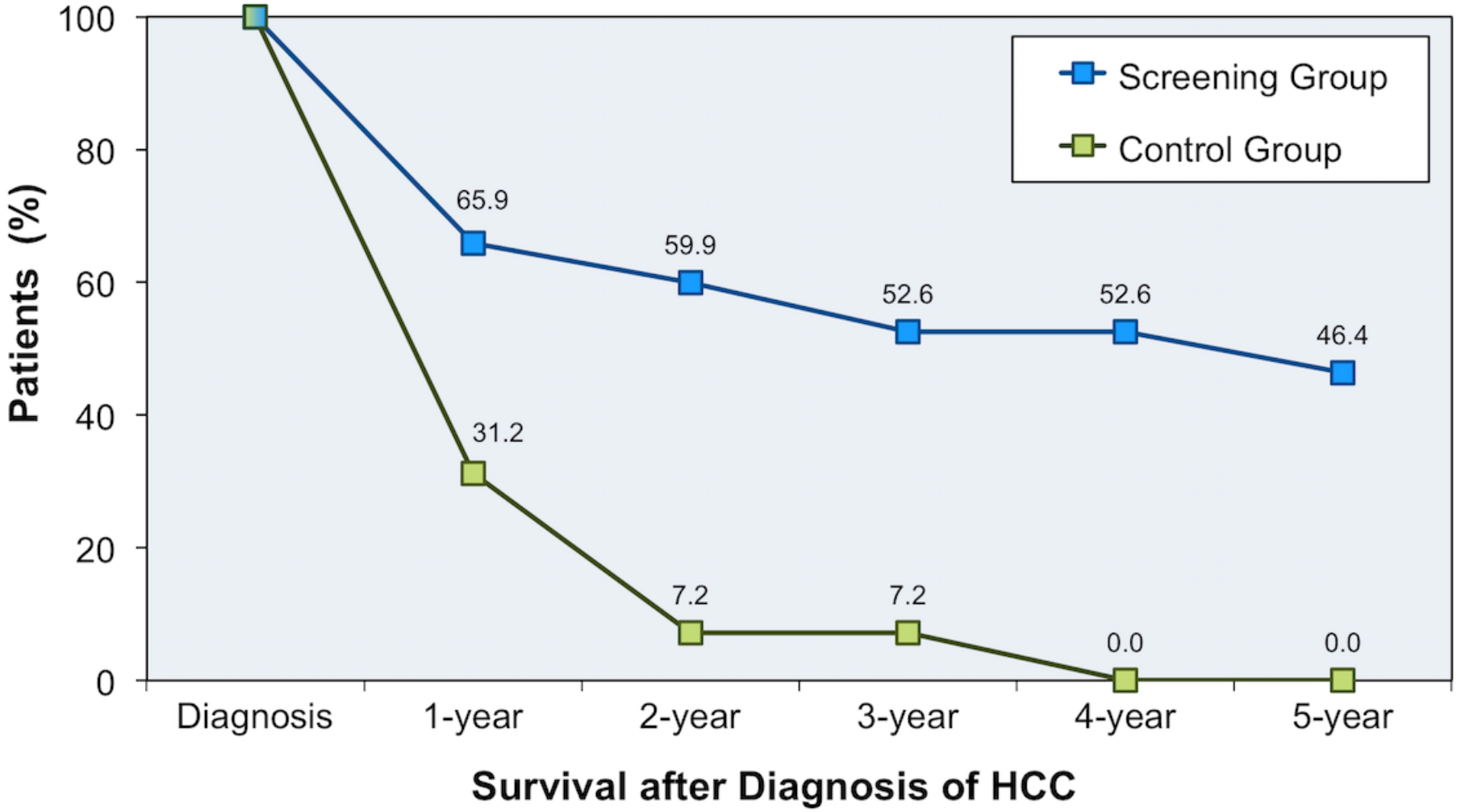
- Patients with Metavir F3-F4 or Ishak 4-6 liver fibrosis , or patients with clinical evidence of cirrhosis and/or Fibroscan > 10 KPa at pre-treatment assessment, should be considered advanced fibrotic patients

- Patients with advanced fibrosis who achieve an SVR should be carefully and periodically monitored for clinical assessment in a specialist Center, in cooperation with General Practitioner

- In all patients with cirrhosis and in those with Fibroscan®>20 KPa and / or a platelet value <150,000 elements/mm3 at pre-treatment baseline, it is strongly recommended to perform an esophagogastroduodenoscopy to evaluate the presence of esophageal varices. Treatment and monitoring of varices do not differ from what is suggested for patients with cirrhosis, according to the Baveno VI indications.

- Patients with advanced fibrosis should remain under surveillance for HCC every 6 months by liver ultrasound, with or without alpha-fetoprotein plasma dosage. It is also indicated a monitoring of liver function, through assessment of laboratory tests and clinical evaluation to calculate the Child-Pugh and MELD scores

http://www.webaisf.org/pubblicazioni/documento-aisf-hcv-2018.aspx



Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol. 2004;130:417-22.

Annual Incidence of HCC in untreated patients with cirrhosis

TABLE 1. PATIENTS AT THE HIGHEST RISK FOR HCC

Population Group	Threshold Incidence for Efficacy of Surveillance (>0.25 LYG; % per year)	Incidence of HCC
Surveillance benefit		
Asian male hepatitis B carriers over age 40	0.2	0.4%-0.6% per year
Asian female hepatitis B carriers over age 50	0.2	0.3%-0.6% per year
Hepatitis B carrier with family history of HCC	0.2	Incidence higher than without family history
African and/or North American blacks with hepatitis B	0.2	HCC occurs at a younger age
Hepatitis B carriers with cirrhosis	0.2-1.5	3%-8% per year
Hepatitis C cirrhosis	1.5	3%-5% per year
Stage 4 PBC	1.5	3%-5% per year
Genetic hemochromatosis and cirrhosis	1.5	Unknown, but probably >1.5% per year
Alpha-1 antitrypsin deficiency and cirrhosis	1.5	Unknown, but probably >1.5% per year
Other cirrhosis	1.5	Unknown
Surveillance benefit uncertain		
Hepatitis B carriers younger than 40 (males) or 50 (females)	0.2	<0.2% per year
Hepatitis C and stage 3 fibrosis	1.5	<1.5% per year
NAFLD without cirrhosis	1.5	<1.5% per year

Abbreviation: LYG, life-years gained.

UO Epatologia – AOUP
Report dei trattamenti con DAAs

Valutazione della efficacia (SVR-12)
Trattamenti avviati al 10/01/2020

	Trattamenti	Valutabili x SVR	%	SVR-12	%	Relapse	%
Totale	**2134**	**1997**	93.6%	**1964**	**98,35%**	**33**	**1,65%**

AIFA	1	2	3	4	5	6	7	8	9	10	11
Pz valutati	678	1	55	322	2	16	298	612	6	6	2
Relapsers	18	0	1	1	1	0	4	7	0	1	0
%	2.65%	-	1.82%	0.31%	50.0%	-	1.34%	1.14%	-	16.67%	-

	Cirrosi + F3	F0-F1-F2	CRIO e Linfomi	IRC / trap. Fegato e altri organi
Pz valutati	**1002**	**910**	**55**	**28**
Relapsers	**20**	**11**	**1**	**1**
%	**2.00%**	**1.21%**	**1.82%**	**3.57%**

Facciamo un po' di conti…

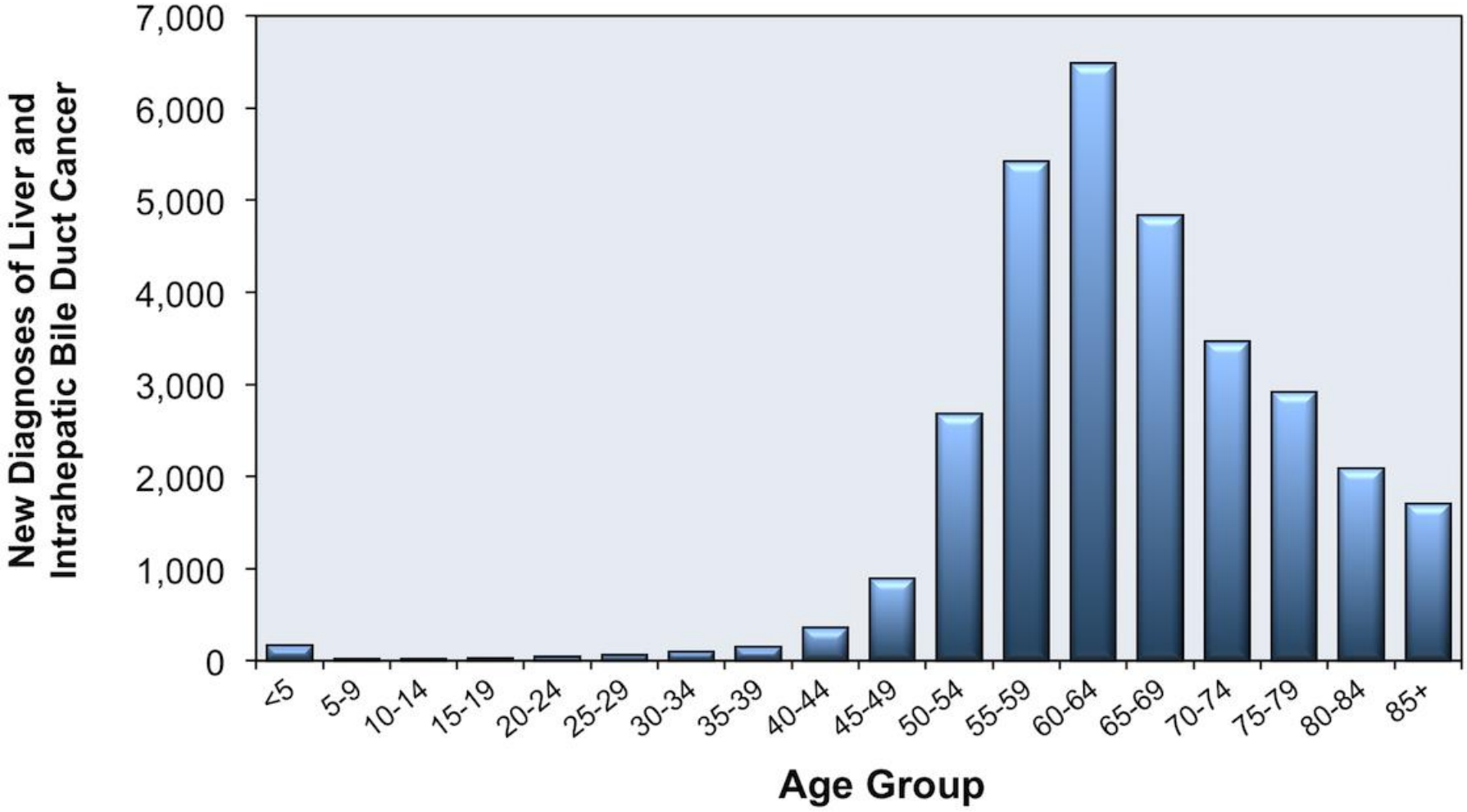
	Pts at risk	% year	HCC n./y	US n./y	US Screening Efficiency (untreated)	US Screening Efficiency (after DAA)
F4-Cirr	678	3-5	30	1356	2.2%	1.1%
F3	322	1.5	5	644	0.8%	0.4%

Paradosso:

→ dopo la SVR l'impegno delle strutture si mantiene elevato, ma si riducono i casi di HCC diagnosticati

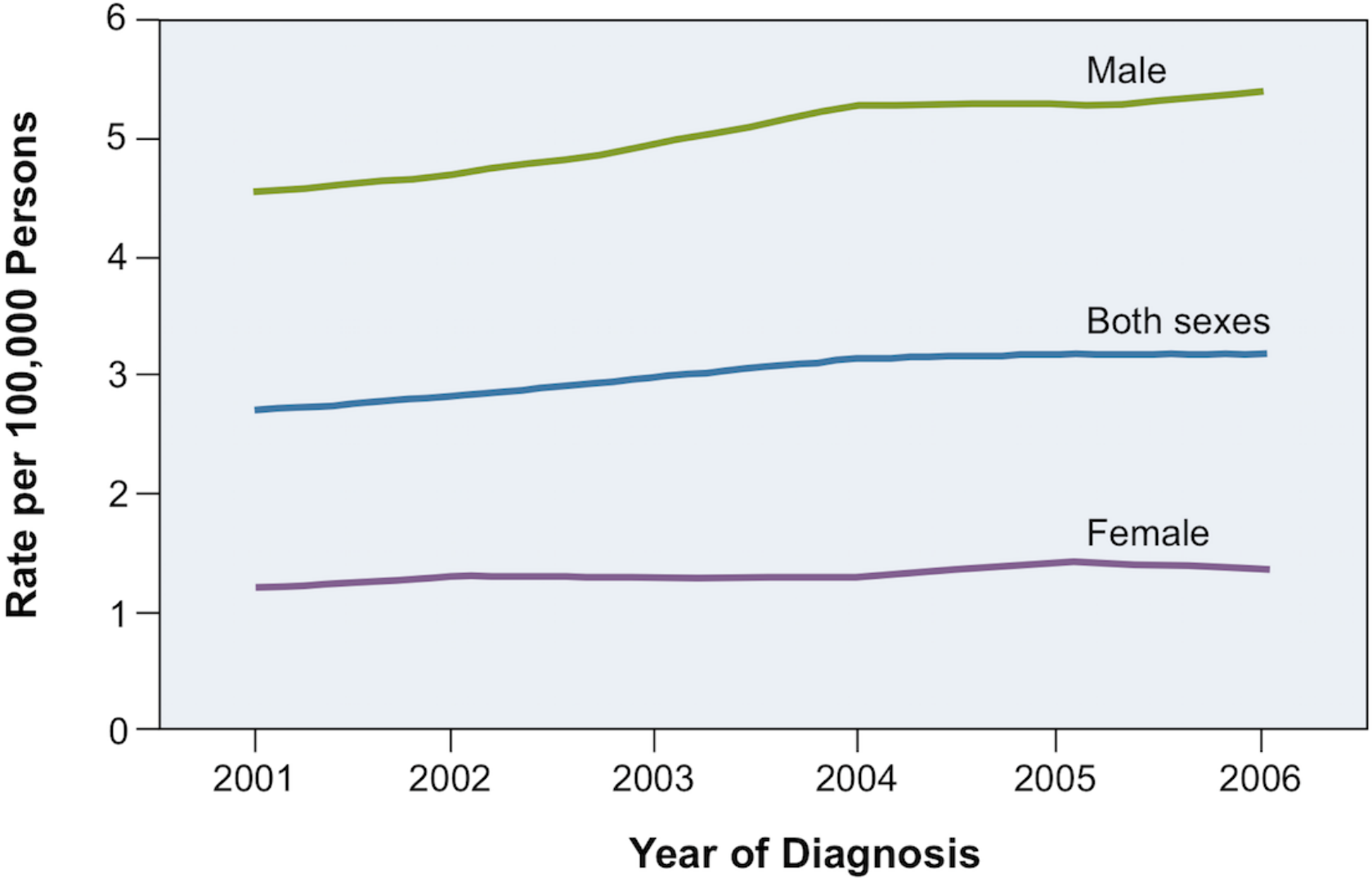
→ Per mantenere efficenza nella sorveglianza sarà necessario sviluppare strumenti che permettano di diversificare i programmi di screening in base al rischio individuale

The role of Age



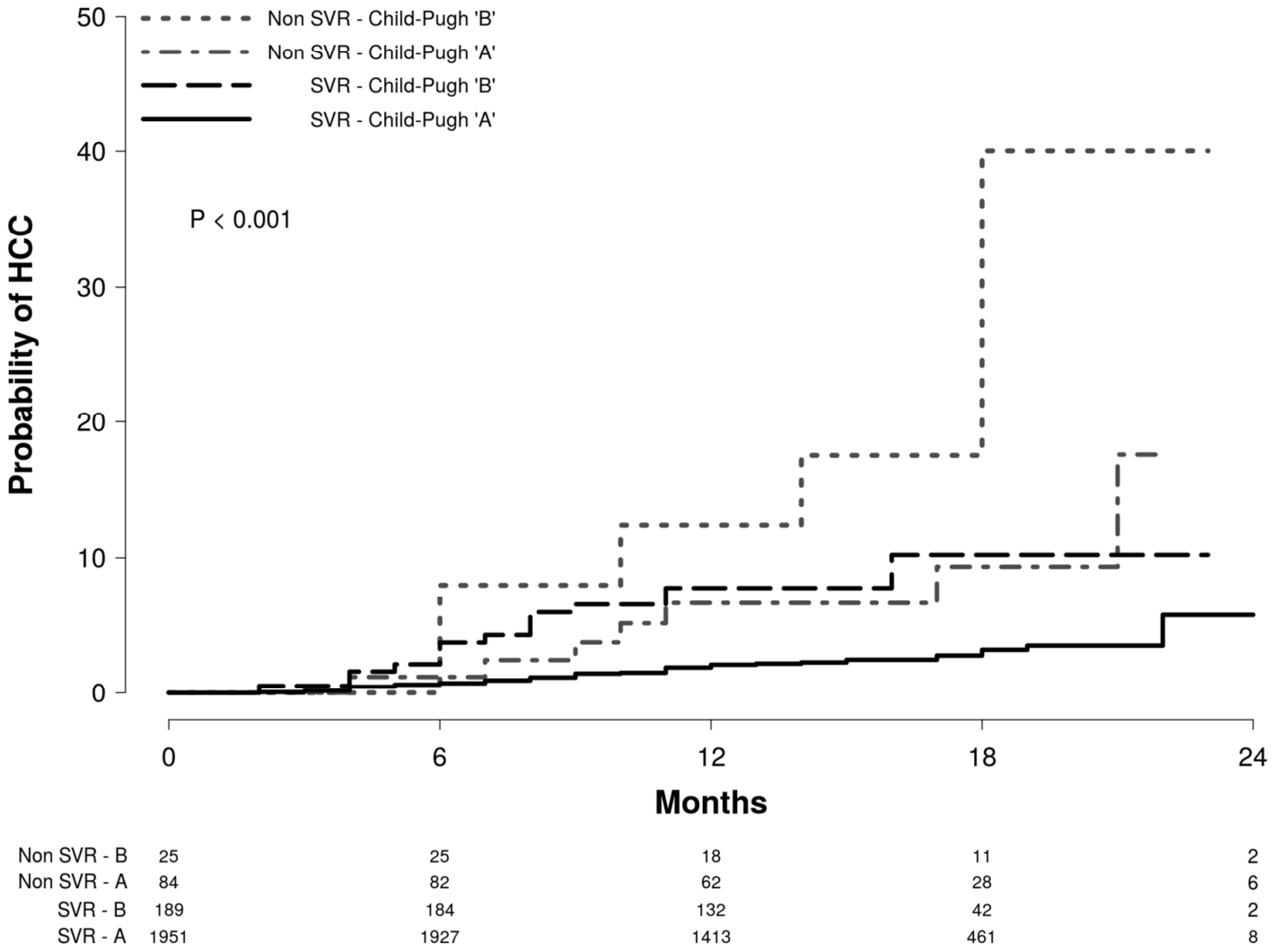
U.S. Cancer Statistics Working Group. United States Cancer Statistics: 1999–2014 Incidence and Mortality Web-based Report. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; 2017.

The role of Sex



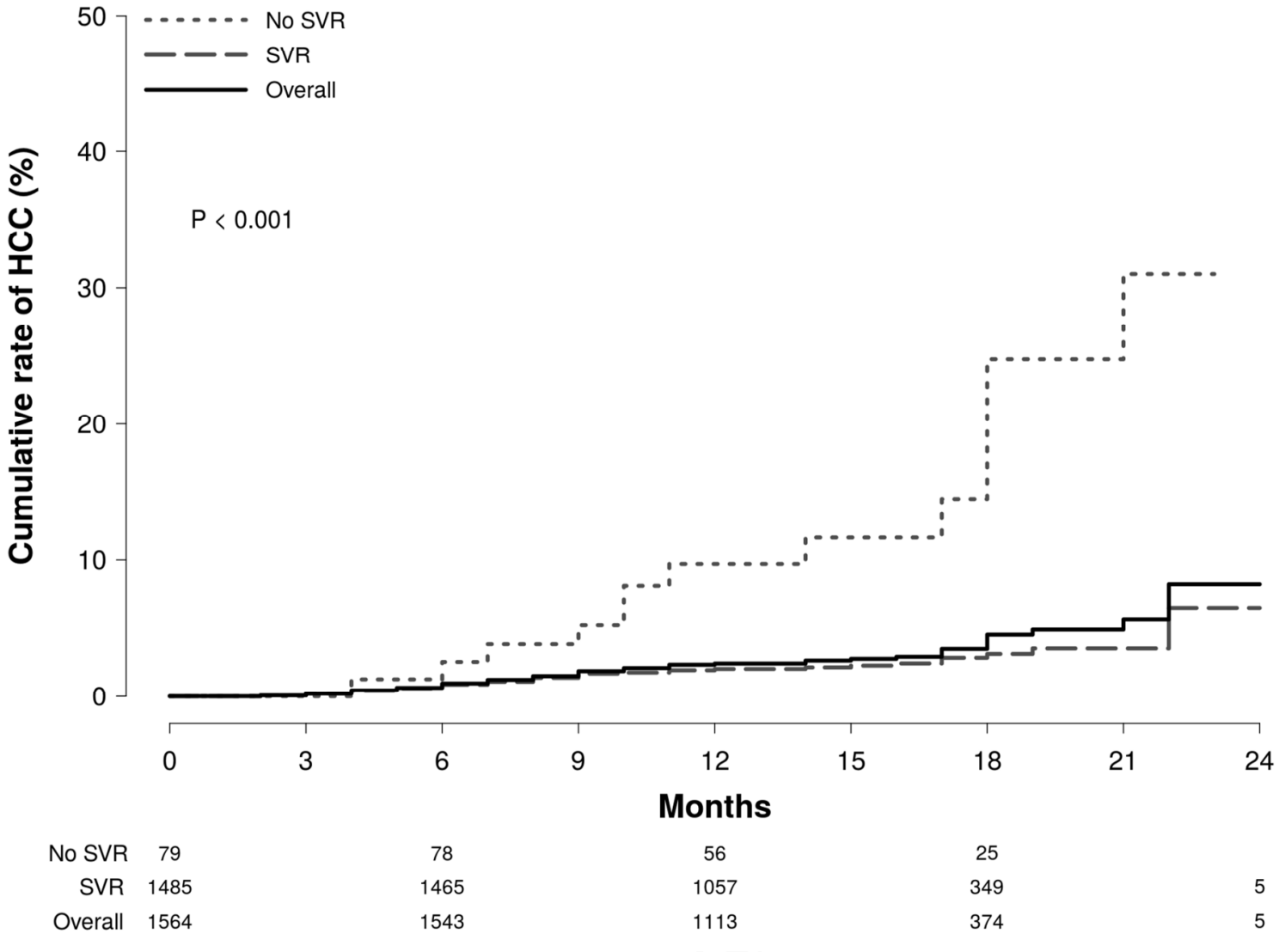
Centers for Disease Control and Prevention (CDC). Hepatocellular carcinoma - United States, 2001-2006. MMWR Morb Mortal Wkly Rep. 2010;59:517-20.

The role of Cirrhosis Stage



Incidence of Hepatocellular Carcinoma in Patients With HCV-Associated Cirrhosis Treated With Direct-Acting Antiviral Agents. Calvaruso, Vincenza Craxì, A. et al. Gastroenterology, Volume 155, Issue 2, 411 - 421.e4

Treatment Failures



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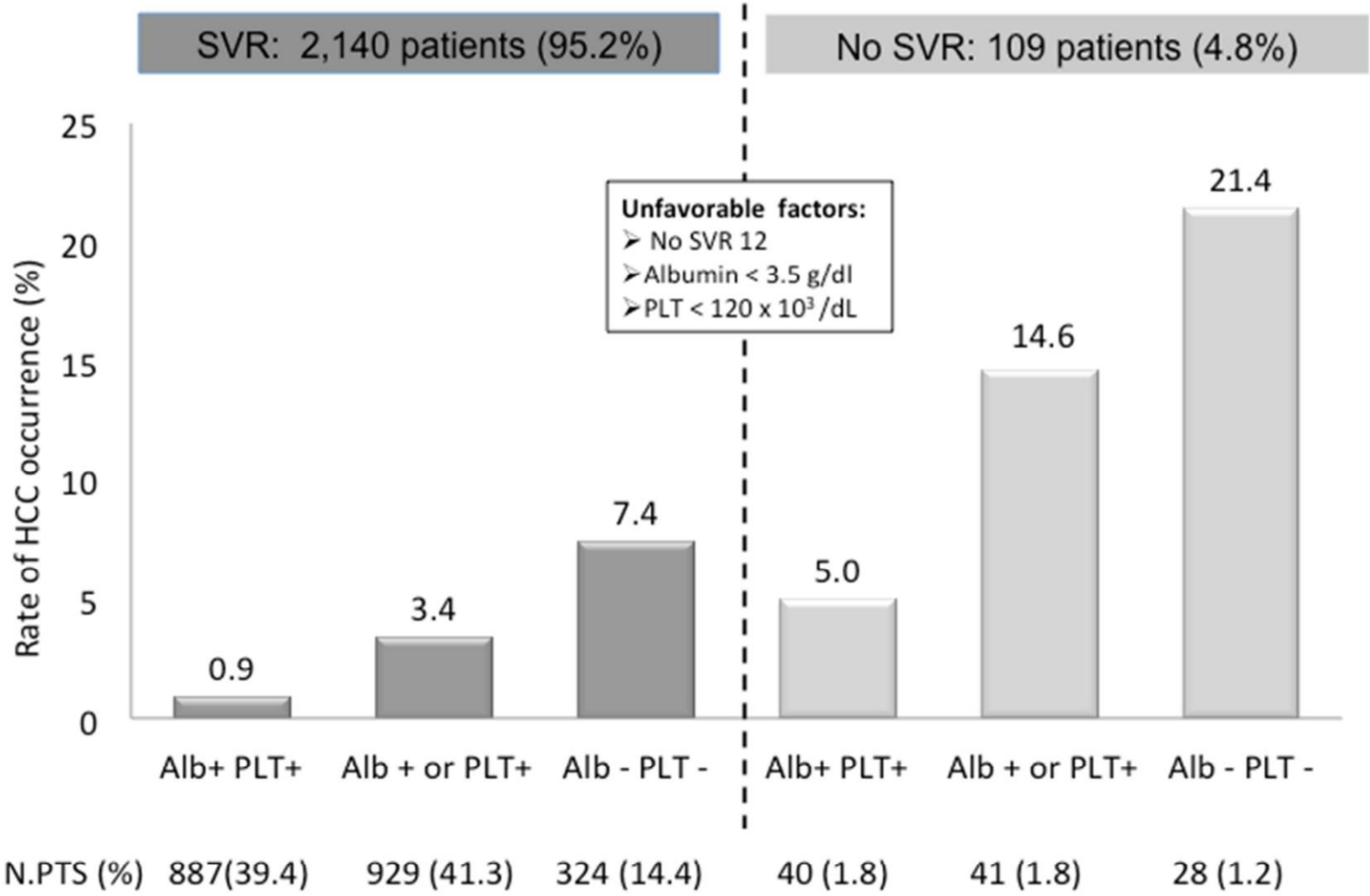
High rate of HCC incidence or progression in cirrhotic patients with DAAs treatment failure: 8/19 (42.1%)

N	Age (y)	Gender	Genot	Pregressa Terapia P/R	Esposizione a DAAs	Fibroscan	Ipertensione portale	Pregresso HCC	Sviluppo HCC	Criterio AIFA	Start Date	weeks	Schedule	Reason for Failure	NS3	NS5A	NS5B	RE-TREATMNET	SVR12
1	76,5	F	1b	NO	FALSE	16	No	FALSE	No	1	01_apr_15	12	SIM+SOF+RBV	Short duration				NO (NHL)	
1	68,8	F	1b	Partial Responder	TRUE	12	Gastropatia congestizia	FALSE	Si, post-trattamento	1	08_apr_15	12	SIM+SOF+RBV	RAS: NS5A e NS5B (?)	wt	L31M, Y93Y/H	C445F	VEL+SOF 12W	YES
2	51,8	M	1a	Non responder	FALSE	39,1	F1	FALSE	Si, post-trattamento	1	14_apr_15	12	SIM+SOF+RBV	RAS: NS3 e NS5A	N174S, D168V	M28V, 32S	wt	LDV+SOF 24W	YES
3	74,8	M	1b	Non responder	FALSE	34,3	Gastropatia congestizia	FALSE	Si, post-trattamento	1	08_mag_15	12	SIM+SOF+RBV	RAS: NS3	168A	wt	wt	VEL+SOF 12W	YES
2	57,9	M	1a	NO	FALSE	75	No	TRUE	Si, Durante trattamento	1	09_giu_15	24	DCV+SOF	Short duration				NO (HCC)	
3	57,6	M	4	Partial Responder	FALSE	75	F1	TRUE	Si, Durante trattamento	5	13_lug_15	24	LDV+SOF	RAS: no	wt	wt	wt	VOX+VEL+SOF	YES
4	68,1	F	1b	NO	FALSE	75	F1	FALSE	No	1	10_ago_15	24	LDV+SOF	RAS: NS5A e NS5B (?)	na	Y93H	559G	NO (Child C)	
4	73,5	M	1b	NO	FALSE	14,3	No	FALSE	No	1	25_feb_16	12	3D+RBV	Short duration				LDV+SOF 24W	YES
6	69,6	M	1b	NO	FALSE		No	FALSE	No	1	22_giu_16	24	LDV+SOF	Short duration				NO (renal failure)	
5	80,4	M	1b	NO	FALSE	12,3	F1	FALSE	Si, post-trattamento	1	27_giu_16	24	LDV+SOF	RAS: NS3 e NS5A	S122T	R30HQ, Y93H	wt	VOX+VEL+SOF	YES
6	79,4	F	1b	No	FALSE	41	NO	FALSE	No	1	20_ott_16	24	LDV+SOF	RAS: NS3 e NS5A	D168I	L28M, Y93H	wt	NO (Child C)	
7	55,2	F	1a	NO	FALSE	13,3	No	FALSE	No	1	26_ott_16	12	SOF+RBV	Inadeguate schedule	wt	wt	wt	NO (D.O.)	
7	66,8	F	4	NO	FALSE	26,7	No	FALSE	No	1	13_apr_17	12	LDV+SOF+RBV	RAS: NS5A	wt	I28M, R30S	wt	VOX+VEL+SOF	YES
8	53,9	M	1a		FALSE	22,8	Gastropatia congestizia	FALSE	No	1	31_lug_17	12	VEL+SOF	RAS: NS5A	wt	Q30H, Y93R/H	wt	VOX+VEL+SOF	YES
9	82,0	M	1b		FALSE	na	na	TRUE	Si, Durante trattamento	1	07_set_17	12	GRZ+EBV	RAS: NS3 e NS5A	Y56H	Y93H	wt	NO (Child C)	
13	80,3	F	1b	NO	FALSE	14,9		FALSE	Si, post-trattamento	1	16_mag_18	12	GRZ+EBV	RAS: NS3 e NS5A	V170I	L28M, Y93H	S556G	VOX+VEL+SOF	YES
14	53,0	M	3		FALSE	21,9		FALSE		1	12_set_18	12	GP	RAS: sequencing ongoing				NO (D.O.)	
12	79,7	F	1b		FALSE	21,8	No	TRUE		1	17_set_18	1,4	GP	Short duration				GRZ+EBV 12W	ongoing
19	45,2	M	3		FALSE	73		FALSE		1	23_apr_19	12	VEL+SOF	RAS: NS5A	wt	Y93H, A62S (sp)	wt	VOX+VEL+SOF	ongoing

Predictors



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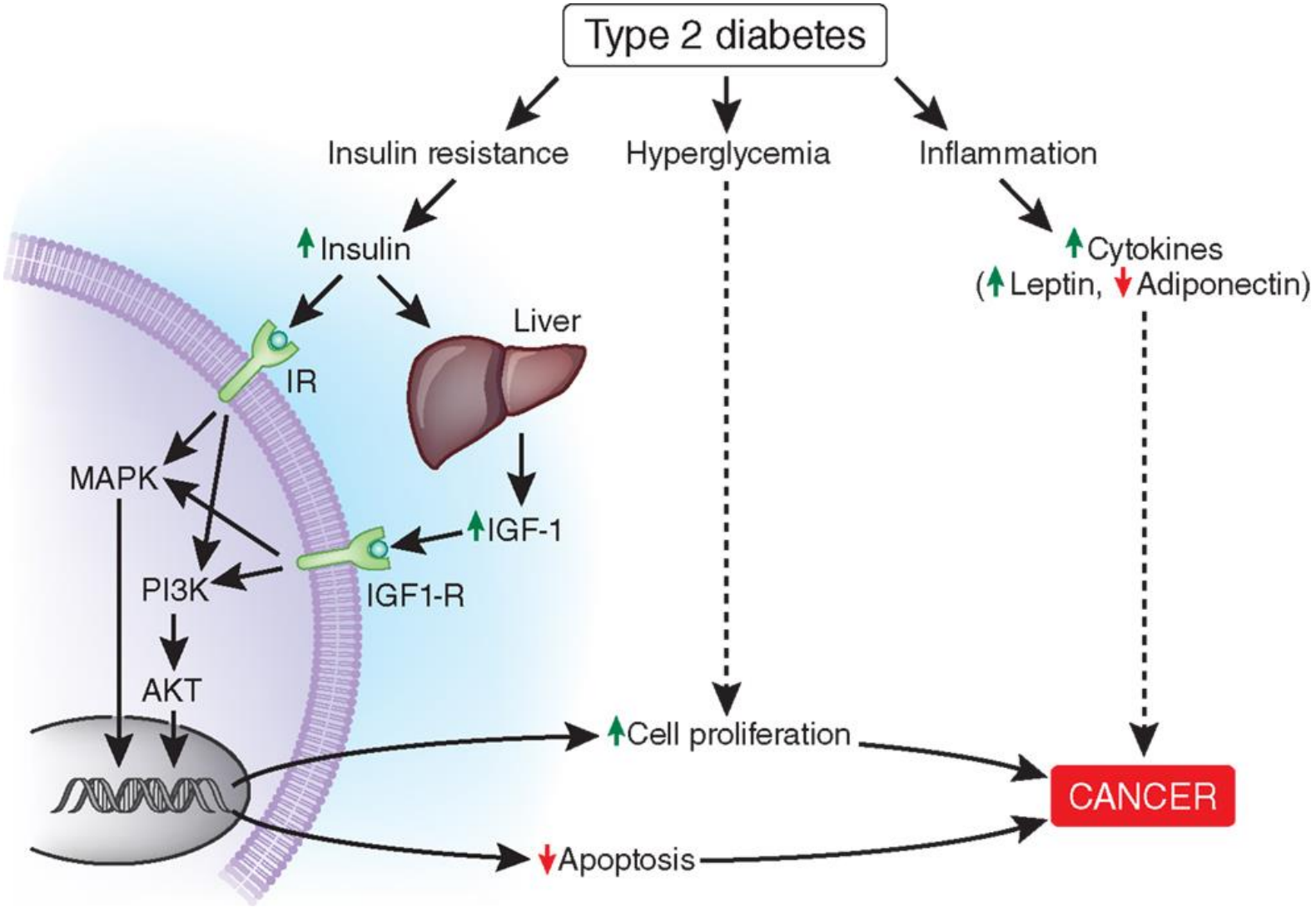
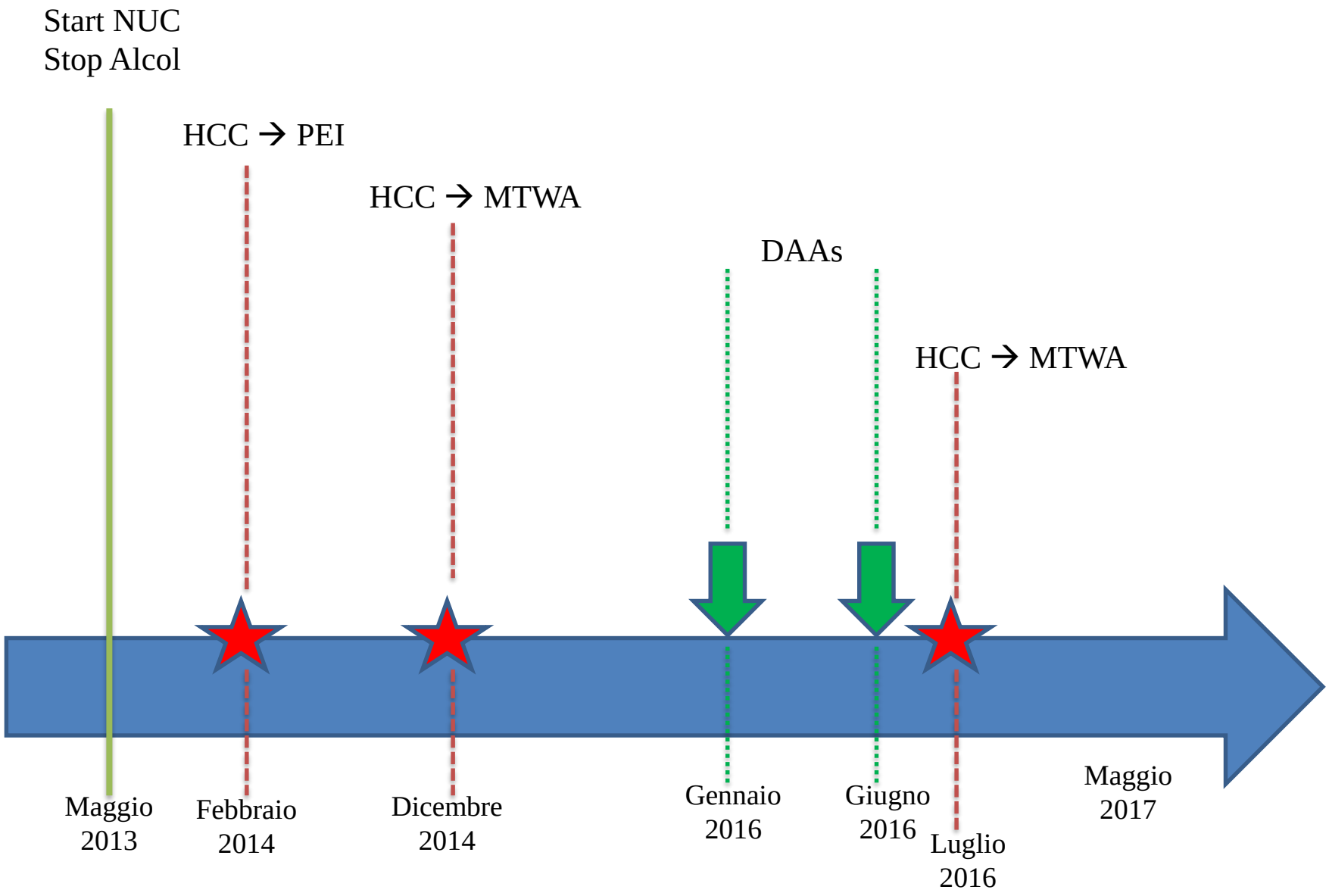
Co-factors


Type 2 diabetes
Insulin resistance
Hyperglycemia
Inflammation
Insulin
Cytokines
(Leptin, Adiponectin)
Liver
IR
MAPK
IGF-1
PI3K
IGF1-R
AKT
Cell proliferation
CANCER
Apoptosis

Alcol, HBV, NASH

D.L. 66 aa maschio



D.L. 66 aa maschio

Familiarità: negativa per epatopatie, patologie metaboliche, CV e neoplastiche

Profilo virologico

- Infezione da **HBV** nota dagli anni 70, riscontrata accidentalmente
- Genotipo D HBeAg neg, anti-HBe pos anti-HDV neg
- Bassi livelli di replicazione virale → **in NUC dal 2013 (dal riscontro di cirrosi)**

-Infezione da HCV nota dal 2013
- Genotipo 3a
- HCV-RNA : elevati livelli viremici (5×10^5 - 8×10^6 UI/mL)

-Screening per HAV positivo

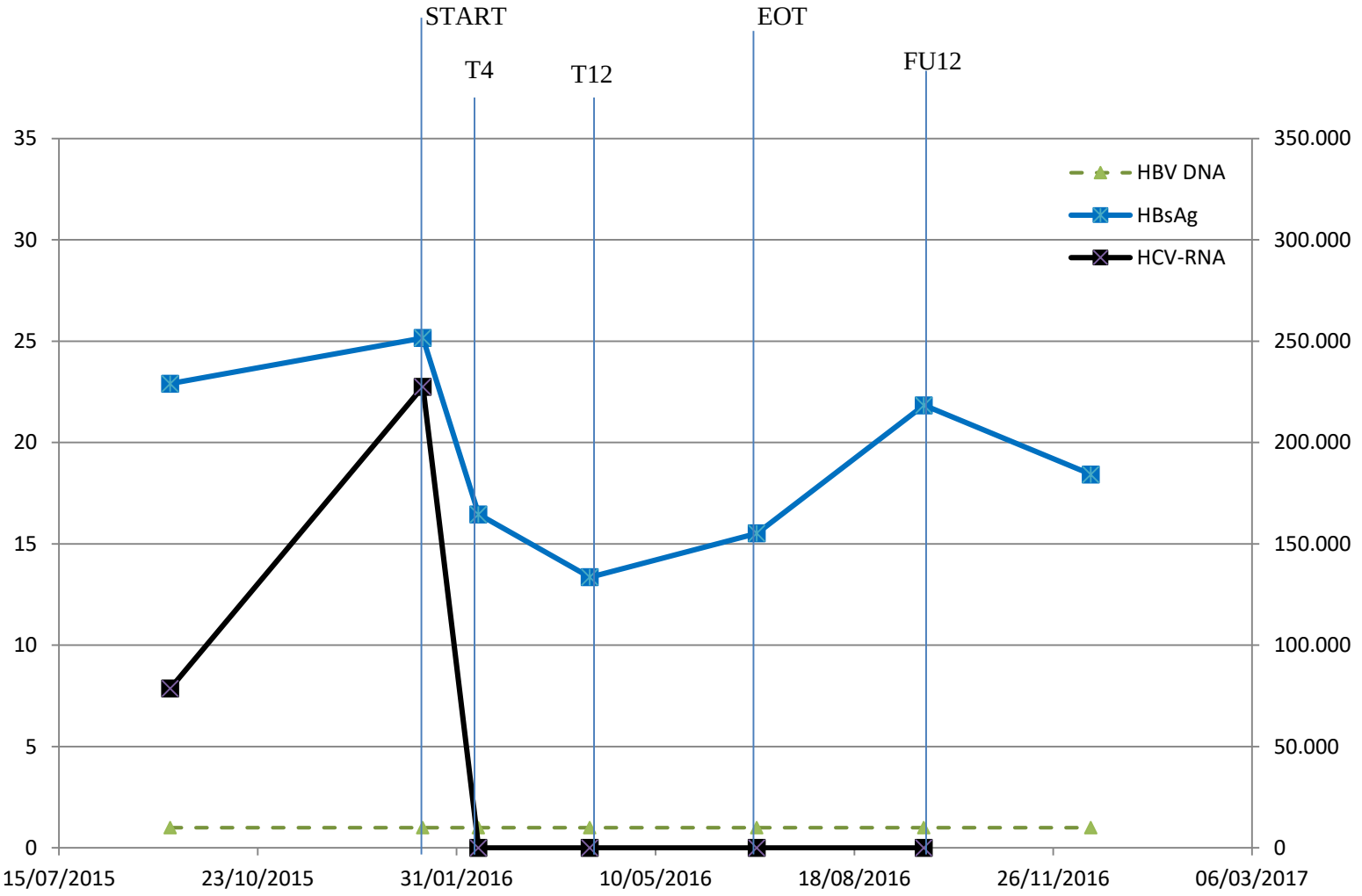
Cofattori di danno epatico

- ***Sovrappeso viscerale*** (max raggiunto 92 kg, **BMI 28.7**)
- ***Alcol*** significativo (fino al 2013 **circa 80 g/die**)
- Autoimmunità: ANA negativi, dosaggio Ig, Fattore reumatoide, VES nei limiti

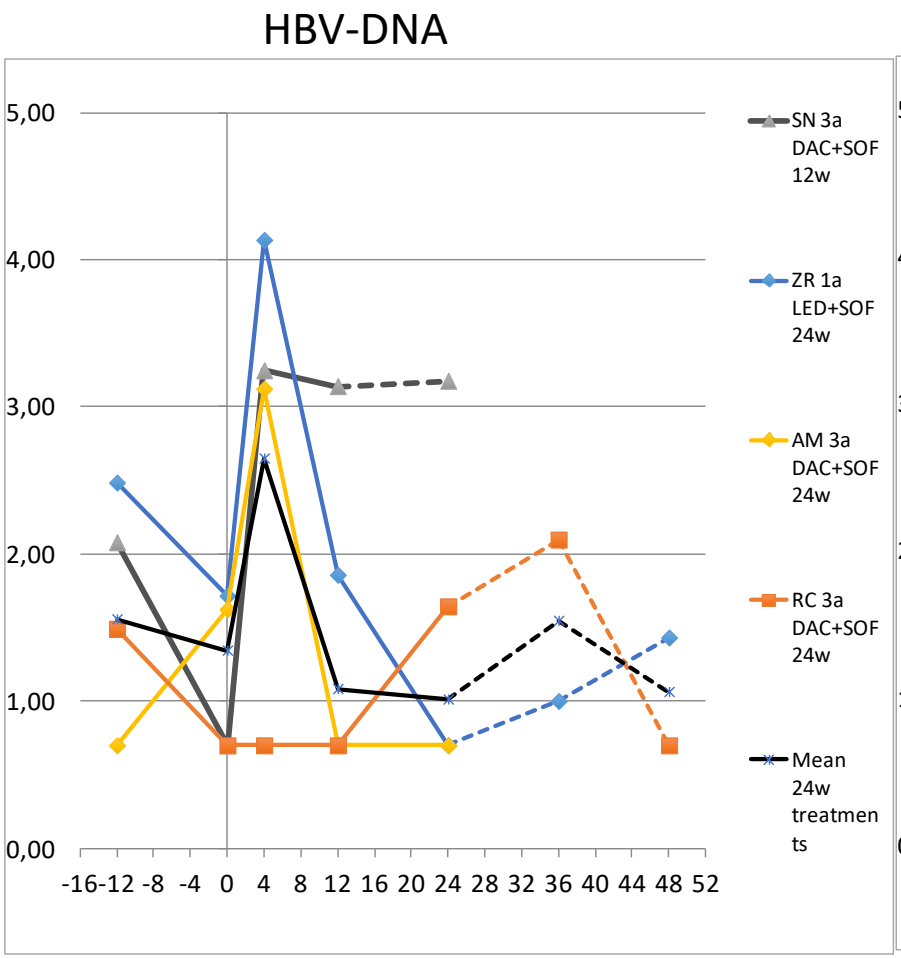
Patologie associate

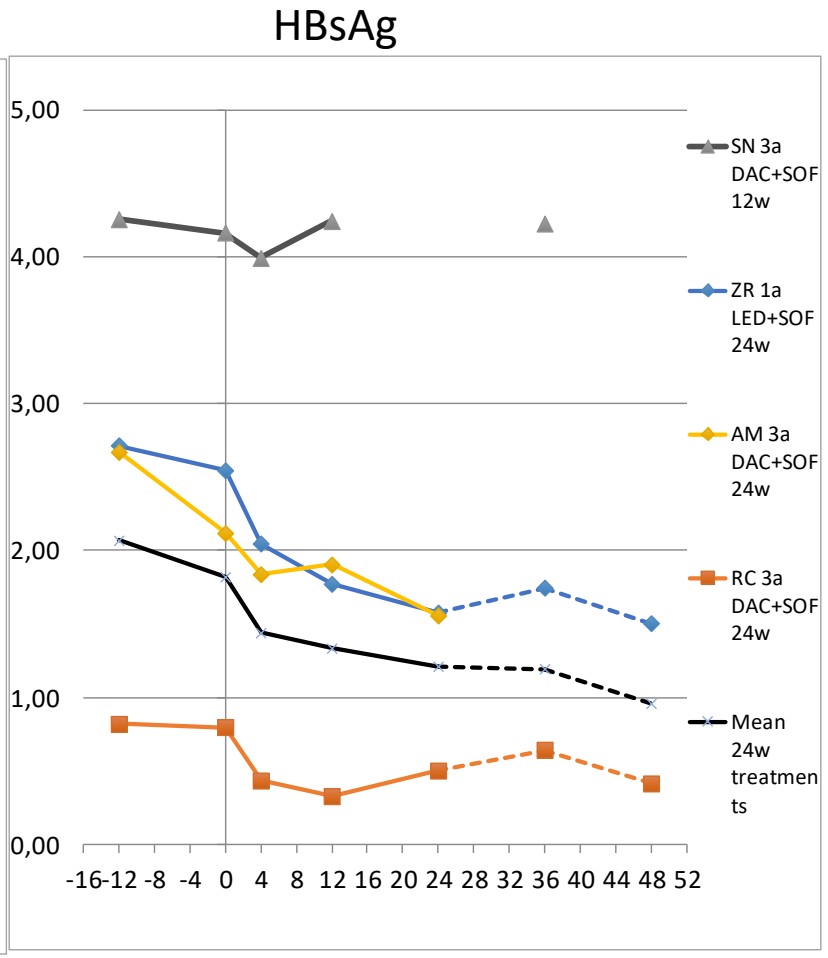
- 2013 : prostatectomia radicale + linfoadenectomia per **adenoCa prostatico**

Cinetica di HBsAg ed HCV-RNA in corso di Terapia con DAAs



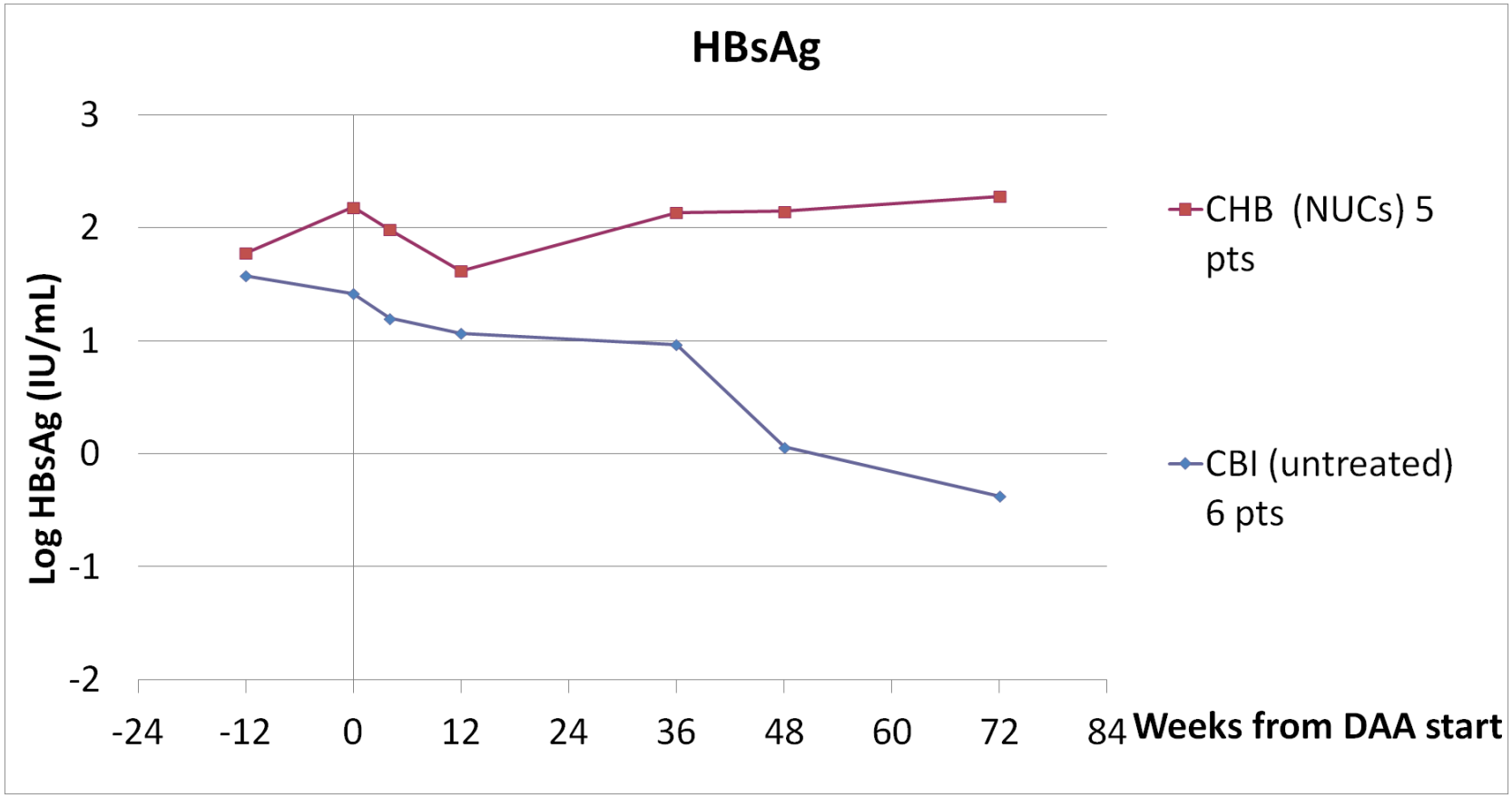
Kinetics of HBV-DNA and HBsAg in patients undergoing DAAs therapy for chronic hepatitis C





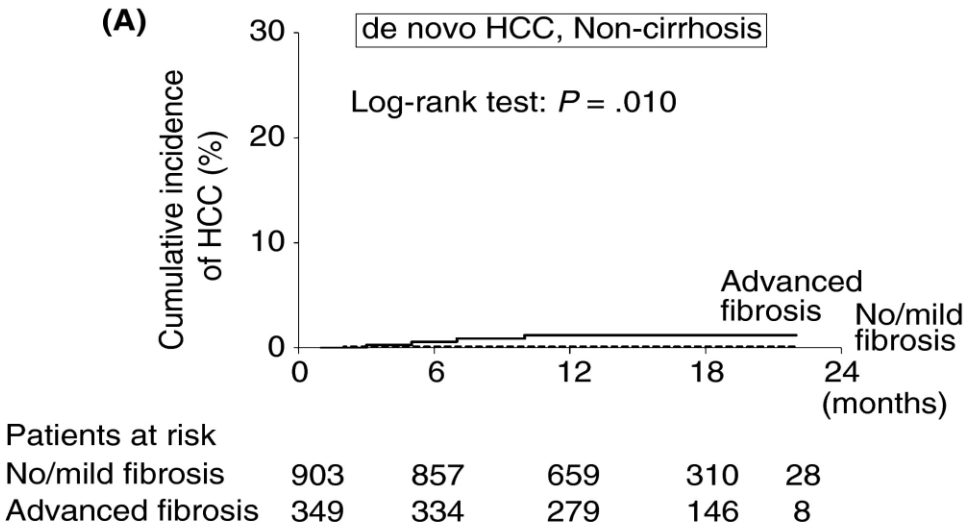
Colombatto et al. AASLD 2017

Lon term HBsAg kinetics in patients undergoing DAAs therapy for chronic hepatitis C

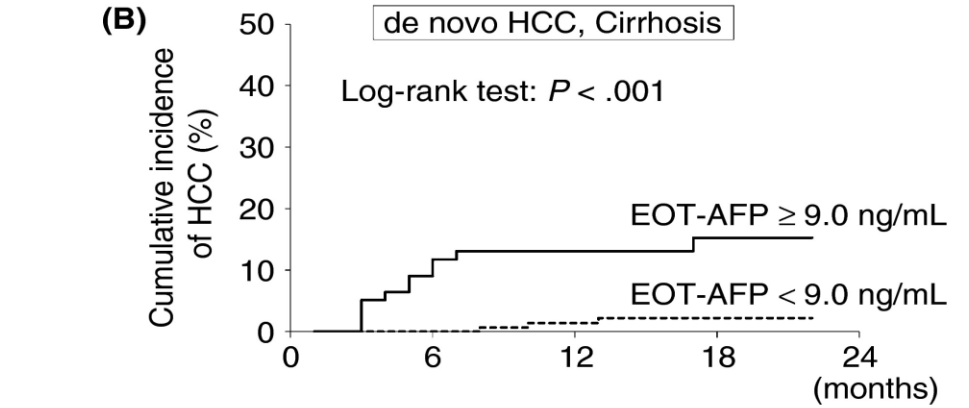


Colombatto et al. AASLD 2017

AFP



Patients at risk					
No/mild fibrosis	903	857	659	310	28
Advanced fibrosis	349	334	279	146	8



Patients at risk					
EOT-AFP < 9	157	152	128	70	1
EOT-AFP ≥ 9	78	65	51	22	2

Ogawa E et al, APT 2018

Follow-up dei noduli displastici

Liver Cancer

Liver Cancer 2017;6:189–203

DOI: 10.1159/000455949

Park et al.: How to Differentiate Borderline Hepatic Nodules in Hepatocarcinogenesis: Emphasis on Imaging Diagnosis

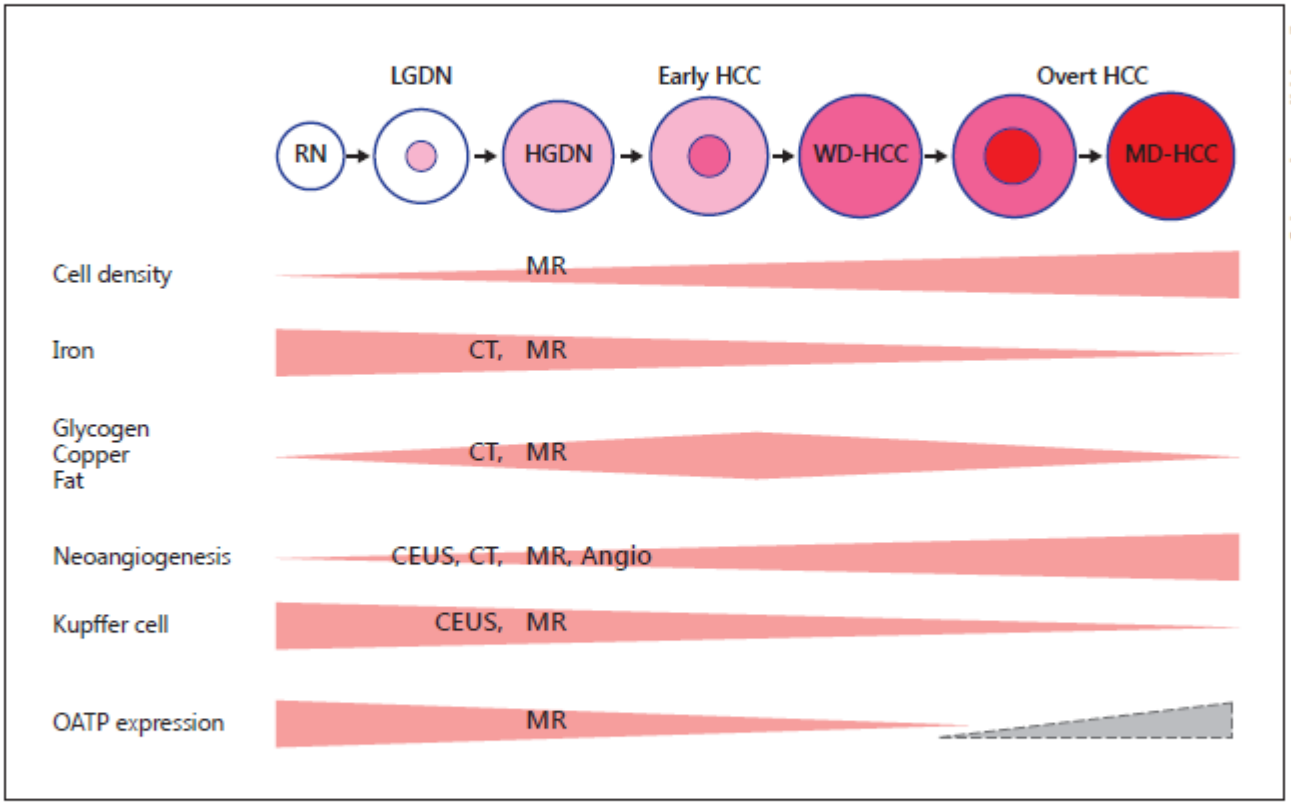


Fig. 1. Cellular and histopathologic changes and tumor visualization on imaging modalities during hepatocarcinogenesis. RN, regenerating nodule; LGDN, low-grade dysplastic nodule; HGDN, high-grade dysplastic nodule; HCC, hepatocellular carcinoma; WD-HCC, well-differentiated HCC; MD-HCC, moderate-differentiated HCC; CEUS, contrast-enhanced US; Angio, angiography; OATP, organic anionic transporting polypeptides. Dotted line in OATP expression indicates paradoxically overexpressed OATP in overt HCCs. Modified figure based on figures from Drs. Kojiro, Kudo, Matsui, Bartolozzi, Lim.

Follow-up dei noduli displastici

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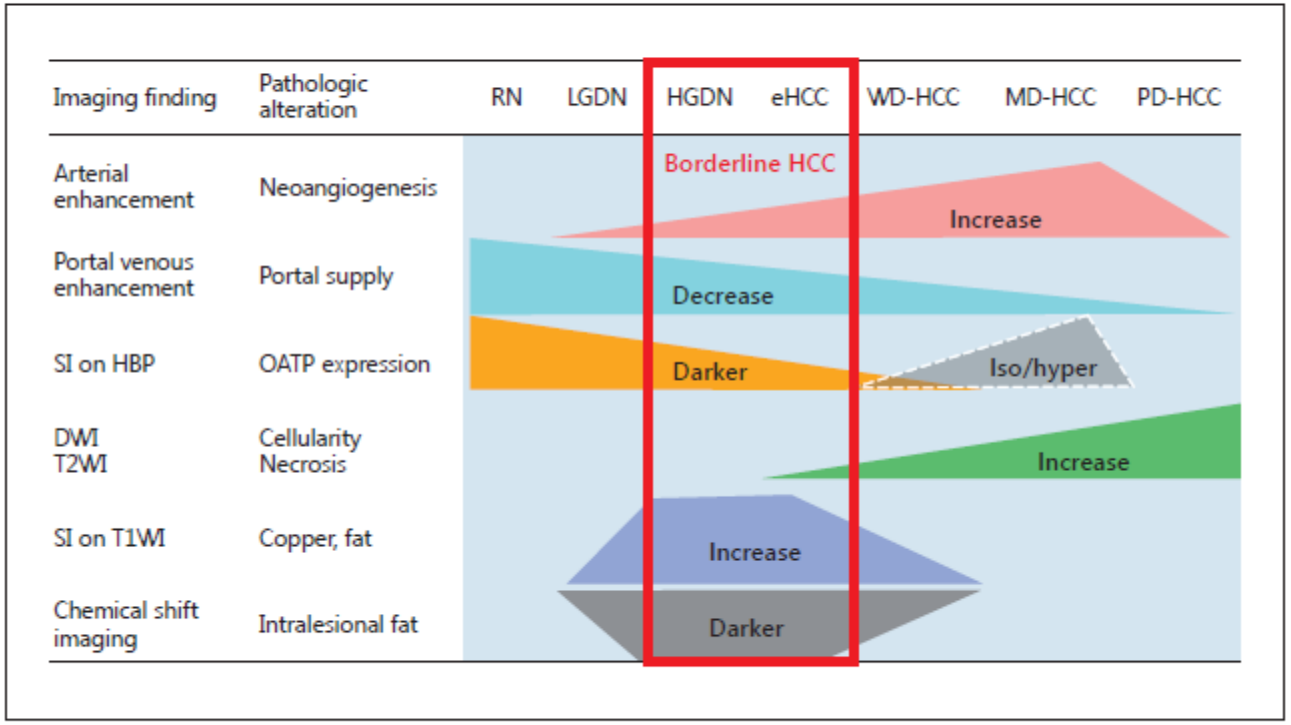

Fig. 4. Imaging features and pathologic alteration during hepatocarcinogenesis.

Post-treatment follow-up: Patients with advanced fibrosis

- Patients with Metavir F3-F4 or Ishak 4-6 liver fibrosis , or patients with clinical evidence of cirrhosis and/or Fibroscan > 10 KPa at pre-treatment assessment, should be considered advanced fibrotic patients

- Patients with advanced fibrosis who achieve an SVR should be carefully and periodically monitored for clinical assessment in a specialist Center, in cooperation with General Practitioner

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- Patients with advanced fibrosis should remain under surveillance for HCC every 6 months by liver ultrasound, with or without alpha-fetoprotein plasma dosage. It is also indicated a monitoring of liver function, through assessment of laboratory tests and clinical evaluation to calculate the Child-Pugh and MELD scores

http://www.webaisf.org/pubblicazioni/documento-aisf-hcv-2018.aspx

Post-treatment follow-up: Patients without fibrosis or with mild or moderate fibrosis

- Patients with no fibrosis or mild-to-moderate fibrosis and without comorbidities at pre-treatment assessment, due to the very low probability of liver disease progression or development of HCC, should be discharged

- Patients with no fibrosis or mild-to-moderate fibrosis and comorbidities (dismetabolic syndrome, obesity, liver steatosis, excessive alcohol intake, autoimmunity, viral coinfections) at pre-treatment assessment, remain at risk of liver disease progression. These patients should be carefully an periodically monitored with non-invasive assessment of liver fibrosis (biochimical tests of liver function, Fibroscan and/or ultrasound)

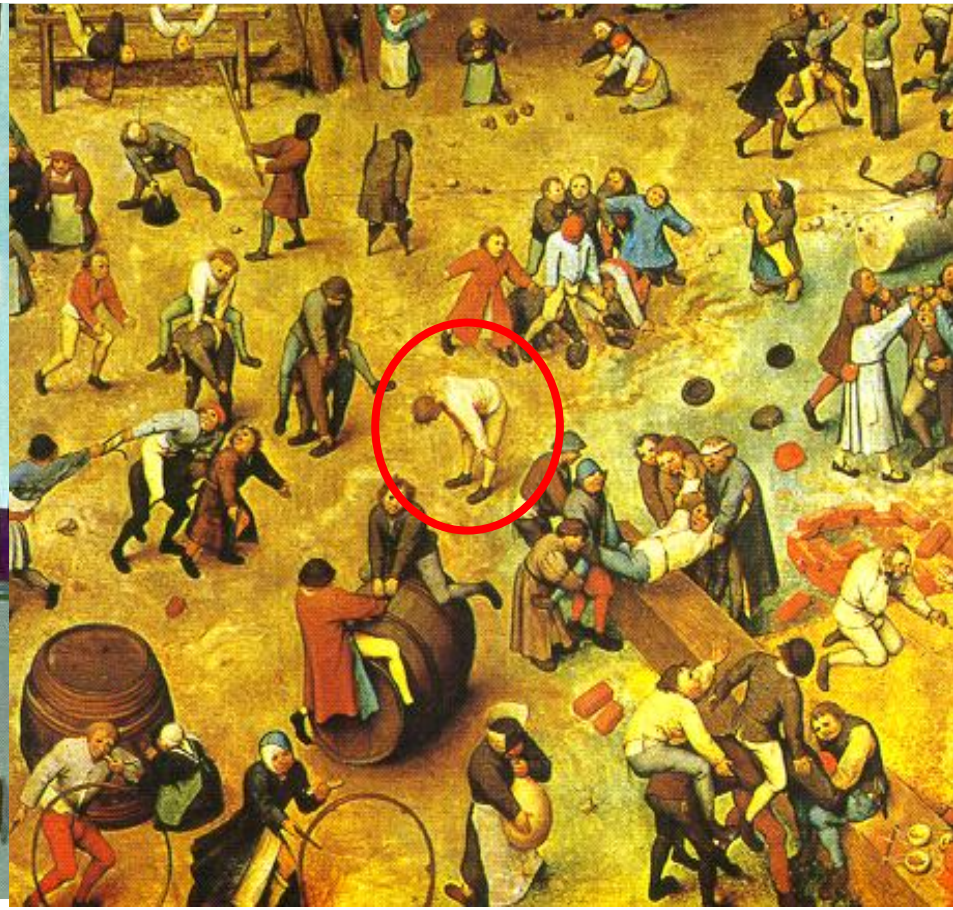
- Patients with HCV extrahepatic manifestations (such as crioglobulinemia), regardless of the presence of cofactors for liver damage, require periodic assessment

http://www.webaisf.org/pubblicazioni/documento-aisf-hcv-2018.aspx

From Medical Practice to Guidelines

Evidence

virtual



Esperience

real

Hepatology Unit
University Hospital of Pisa, Italy

Director: prof. Maurizia R. Brunetto

Medical Doctors

Barbara Coco
Piero Colombatto
Filippo Oliveri
Veronica Romagnoli
Antonio Salvati
Gabriele Ricco
Lidia Surace
Riccardo Gattai
Pietro Ciccorossi

Nurses

Antonella Cristofani
Simonetta Ferretti (part-time)
Simona Giannetti
Teresa Crisponi
Barbara Zucchelli
Raffaele Apuzzo

Administrative Personel

Arianna Del Chicca

Biologists

Daniela Cavallone
Francesco Moriconi

Bio-Physics

Luigi Civitano
Ranieri Bizzarri

INNOVATIVE MODEL OF PERSONALIZED CARE

Ferruccio Bonino
UPMC Institute for Health
Chianciano