VI Corso Nazionale di Ecografia Clinica SIEMC

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“ Ruolo dell’Ecografia nella nuova Epidemiologia delle Epatopatie diffuse ”

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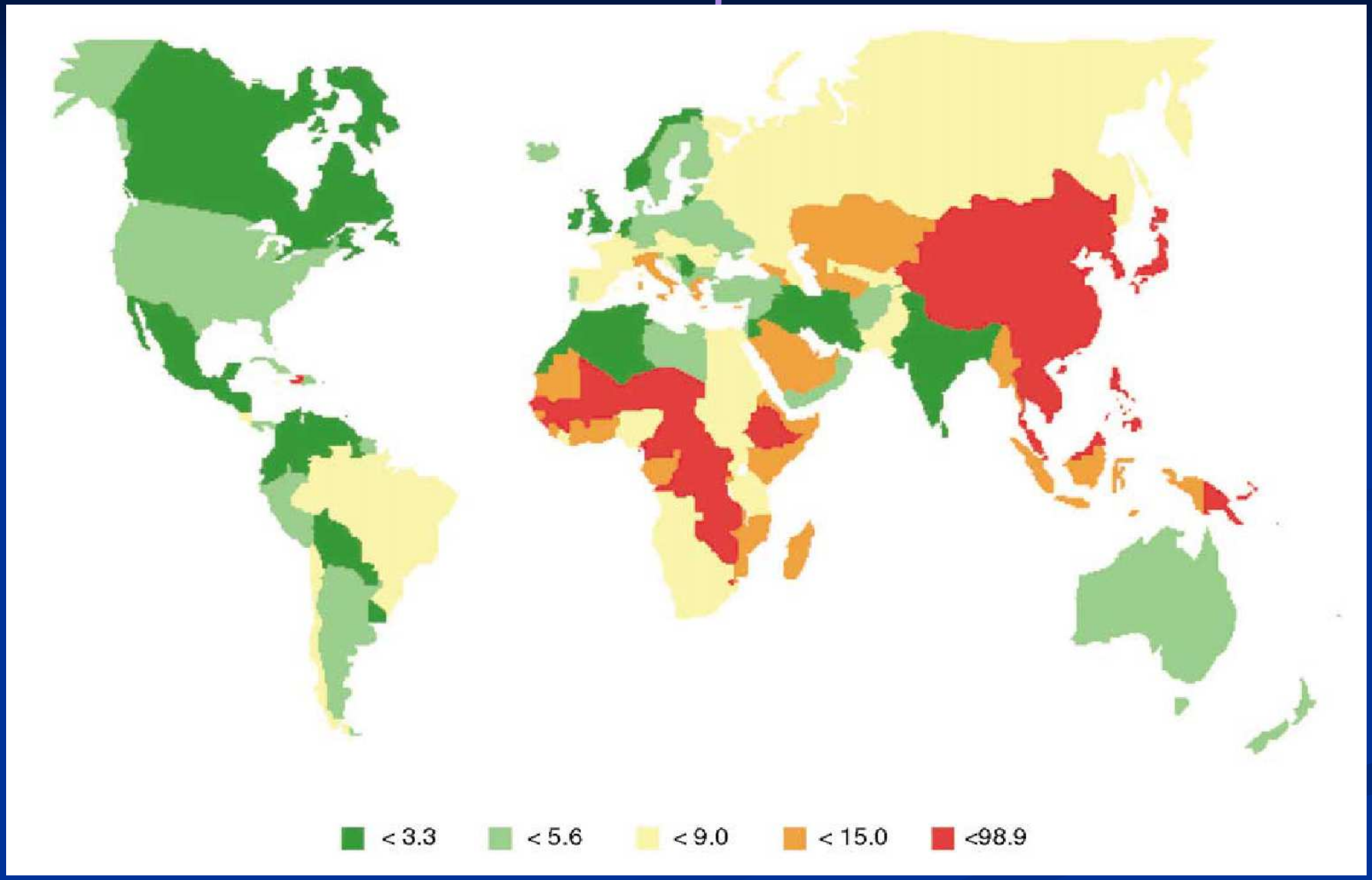
HCV epidemiology in 2011: estimation of number of patients ever infected

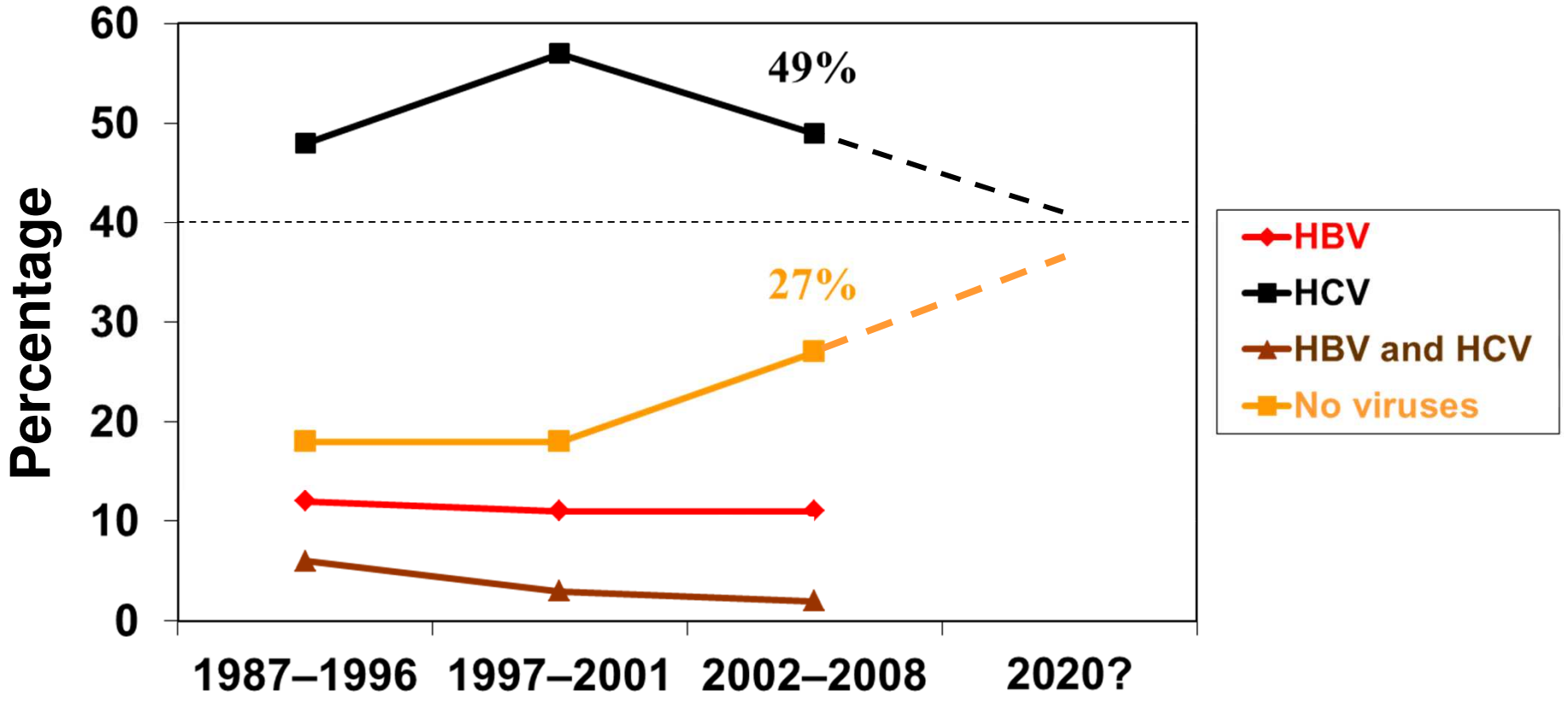
Deuffic-Burban S, et al. Gastroenterology 2012 Oct;143(4):974-85.e14

Hepatocellular Carcinoma (HCC) incidence / 100.000



Etiology of HCC in Italy: observed and expected temporal trends

11 centers, 3027 patients, recruitment period 1987–2008



Santi V. et al., for ITA.LI.CA, J Hepatol 2012;56:397-405

Rischio annuale (per 100 per anno) di sviluppo di HCC su cirrosi

(Kanwal F, Singal AG, Gastroenterology 2019)

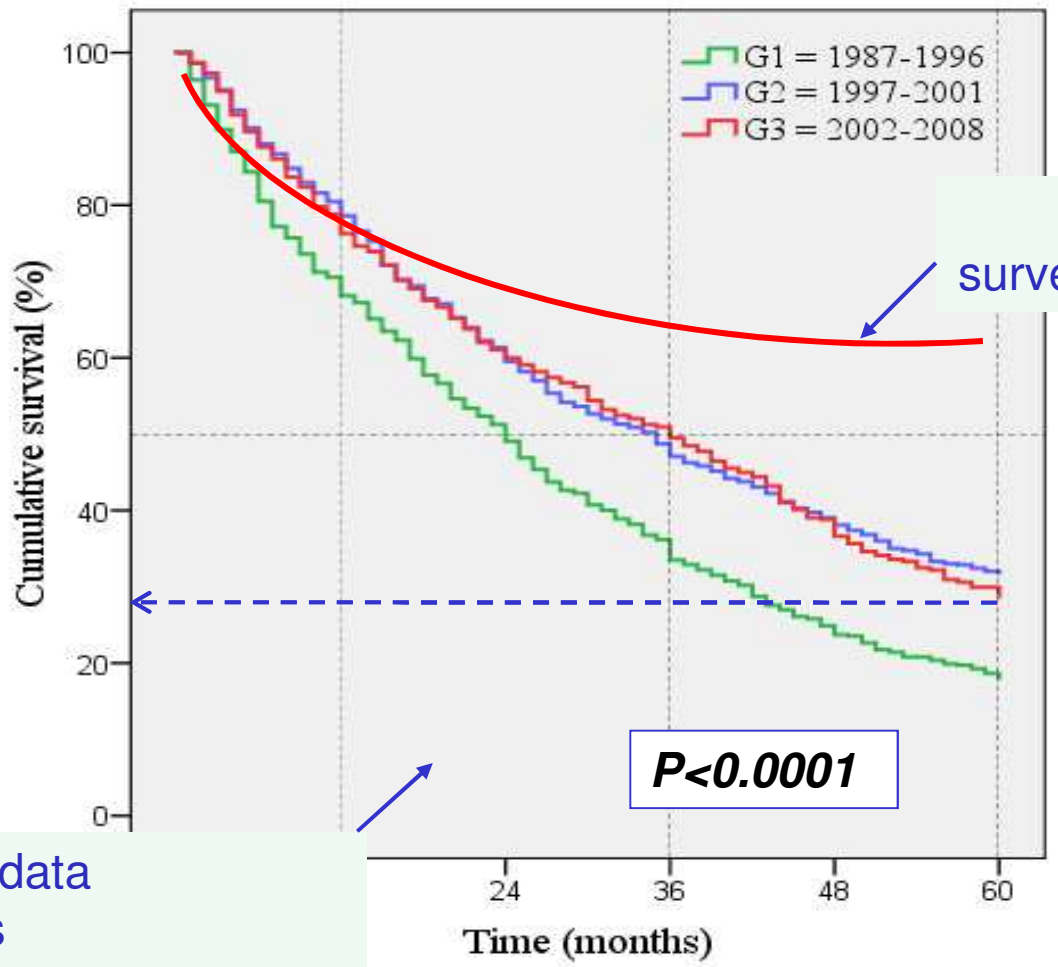
- HCV/HBV non trattate 2,4

Fattori di rischio emergenti :

- HCV trattata 1,8
- HBV soppressa 1,3
- NAFLD 1,0

Survival of HCC patients in ITA.LI.CA

ITA.LI.CA database 2008



Nationwide surveillance programs

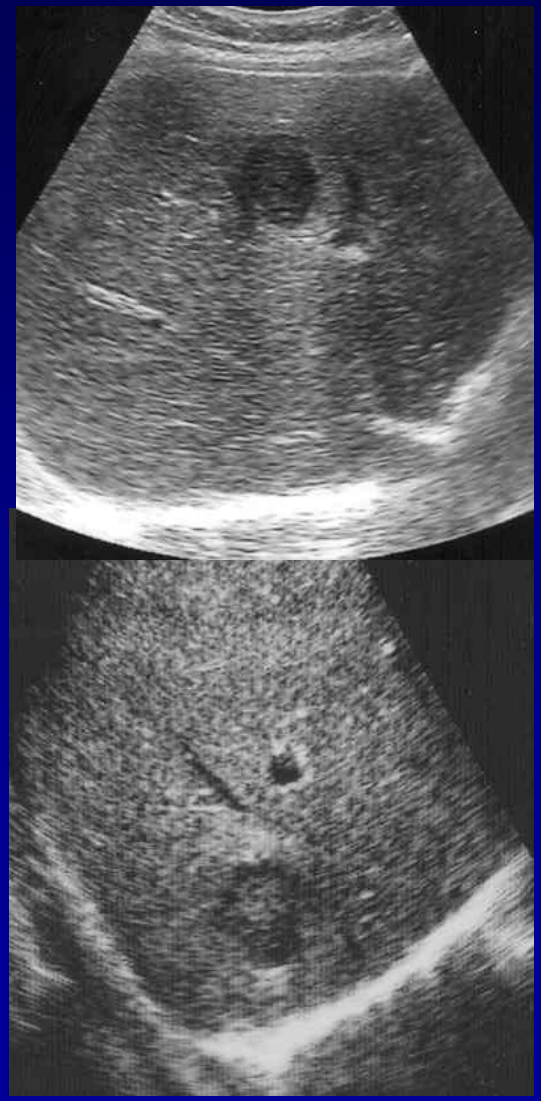
P<0.0001

- HCC specific data
- Selection bias
- State-of-the-art management
- Surveillance rate

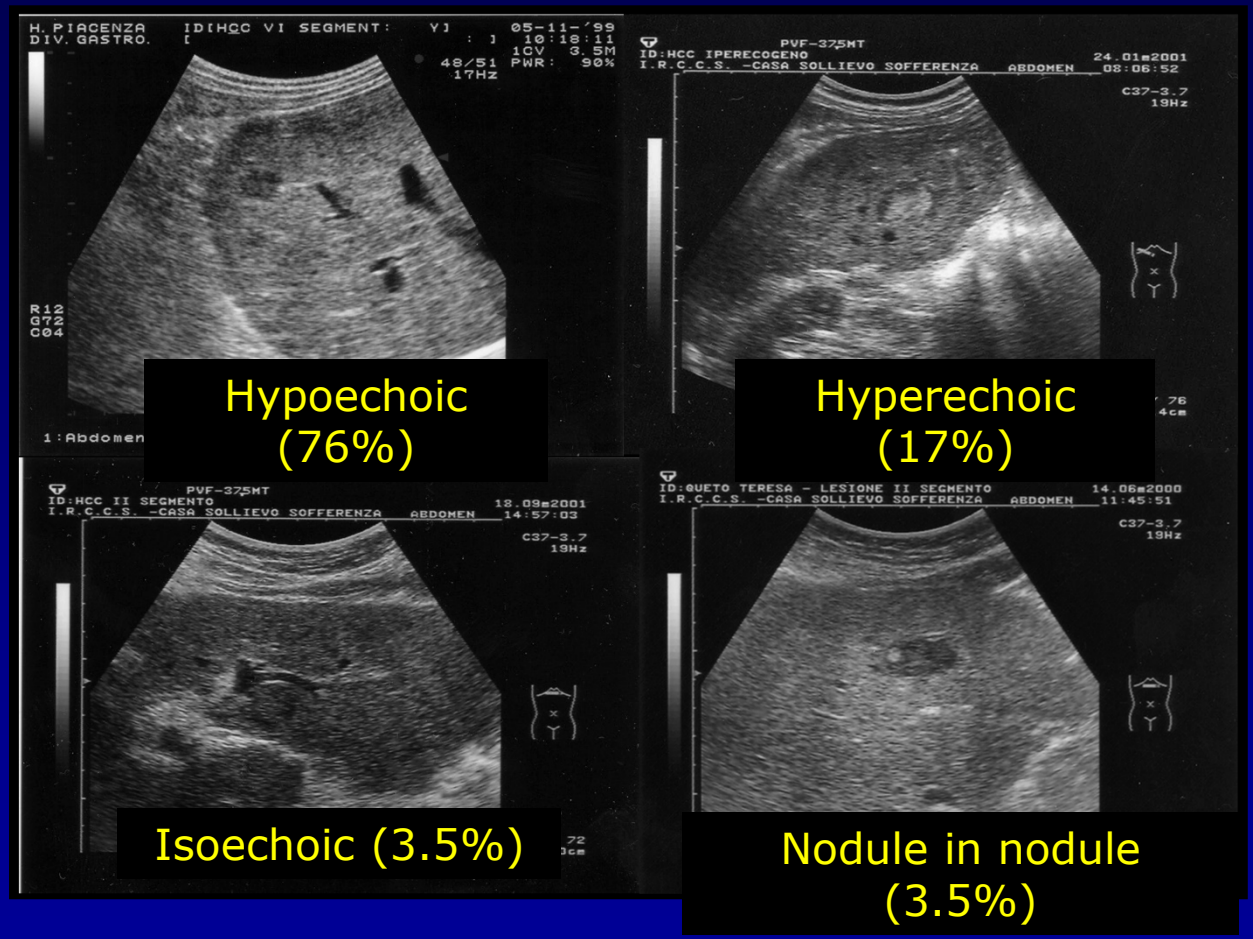
Santi V. et al., for I TA.LI.CA, J Hepatol 2012;56:397-405

US detection of HCC

location

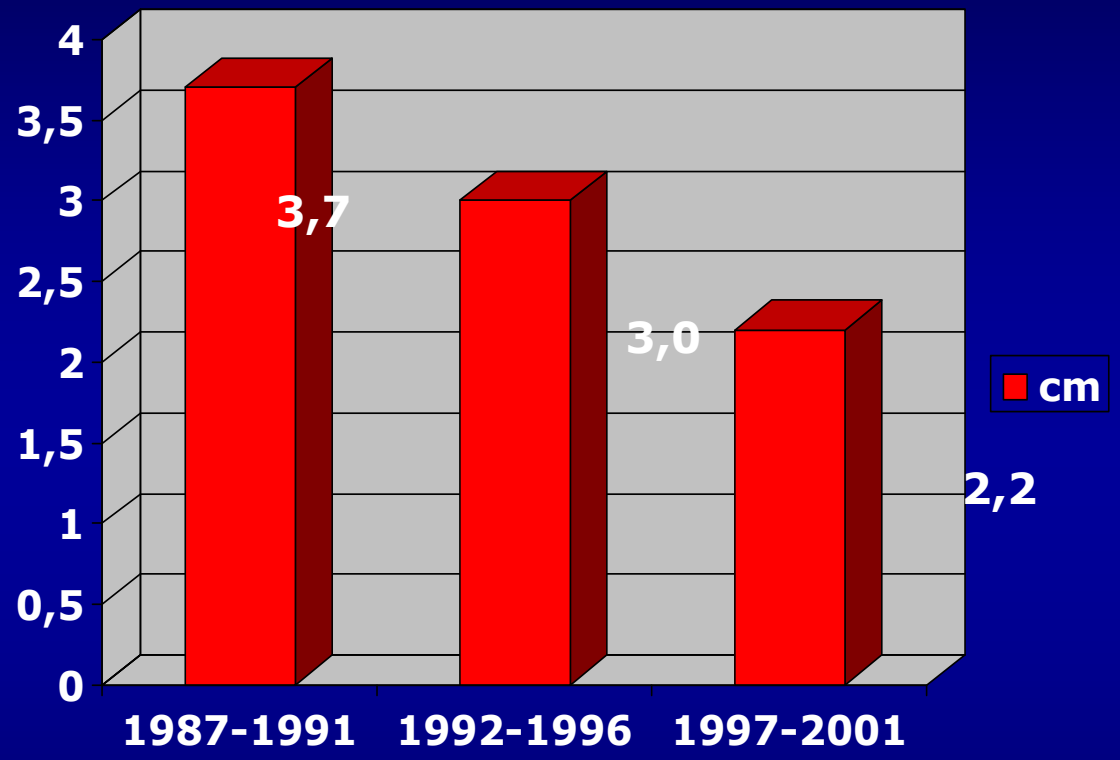


pattern (nodules < 2 cm)



Rapaccini GL, Liver Int 2004

Mean diameter of HCC diagnosed by screening during three successive 5-year periods (417 cirrhotics)



Sangiovanni A, Gastroenterology 2004

Sorveglianza per la diagnosi di HCC «early»

- US ± αFP ogni 6 mesi : l'intervallo di 3 mesi non aumenta il numero dei casi «early» e non migliora l'accessibilità ai trattamenti (Trinchet JC, Hepatol, 2011)
- La sorveglianza con TC non migliora sensibilità e specificità, senza significativa differenza rispetto a US

  (Pocha C, Aliment Pharmacol Ther, 2013)
- La sorveglianza con RM aumenta il numero di diagnosi di early HCC, ma non è cost-effective

  (Kim SY, JAMA Oncol, 2017)

↓

« ..uso routinario di US e αFP ogni 6 mesi nella sorveglianza per HCC su cirrosi»

(Lee E, Clin Gastr Hepatol,2013 ; Tzartzeva K, Gastroenterology, 2018)

Le diverse "ere" della terapia anti - HCV

IFN (< 30%)

↓

IFN + RIBA (< 50%)

↓

IFN + RIBA + DAA 1° g (70 – 80 %)

↓

DAA (IFN free)

> 90 %

Trattamento antivirale per l'infezione da HCV

- *SVR : HCV-RNA non dosabile dopo 12-24 settimane dalla fine del trattamento (recidiva infrequente)*
- *Fattori prognostici della SVR : genotipo*
  carica virale
  polimorfismo IL28B
  grado della fibrosi
  insulino-resistenza
- *I dati disponibili su incidenza e ricorrenza di HCC a lungo termine nei pz trattati derivano prevalentemente dagli studi su IFN ± RIBA*

↓

Assioma : SVR = prevenzione HCC (?)

Sviluppo di HCC : cfr SVR+ / SVR-

- *Van de Meer,Jama 2012: 10-yrs incidence → SVR+ = 5,1%*
  SVR- = 21,8%
- *Morgan, Ann Int Med 2013 (31.528 pz SVR+) → rischio relativo = 0.24 in pz con epatopatia a qualunque stadio*
  0.23 in pz con fibrosi avanzata (F3, cirrosi)
- *Yu, Antivir Ther 2006 → l'incidenza di HCC non differisce tra pz non sottoposti a terapia e pz in cui la terapia ha fallito*
- *Singal Clin Gastr Hepatol 2010 → in pz con viremia persistente il prolungamento del trattamento con IFN non riduce il rischio di HCC*

↓

SVR = riduzione incidenza di HCC è un'equazione ?

Equazione « SVR = ridotto rischio di HCC »

IFN ± RIBA → SVR → ridotto rischio di HCC = ***DAAs*** *→*
SVR → ridotto rischio di HCC ??

- *IFN : attività antiproliferativa di per sé..*
- *La SVR riduce ma non elimina il rischio di HCC : la fibrosi severa (cirrosi) è il singolo più importante fattore di rischio di HCC anche dopo SVR (Makiyama, Cancer, 2004)*
- *L'età (durata della malattia cronica di fegato) è un altro significativo determinante dello sviluppo di HCC*
- *Un processo di carcinogenesi epatica può iniziare prima dell'inizio del trattamento antivirale (e non essere visibile alle tecniche diagnostiche …)*

Reig M et al. « Unexpected tumor recurrence in patients with HCV-related HCC undergoing IFN-free therapy : a note of caution» (J Hepatol, april 2016)

- 103 pts with prior HCC

- 58 pts with inclusion criteria : - HCC treated prior DAA
  - Complete response to curative
  - DAA starting withouth HCC or non characterized nodules
  - SVR12 = 97,5%
- 55 pts cirrhotic
- Median follow-up : 5,7 mth
- Radiologic tumor recurrence : 16 pts (27,6% !)

Cammà C et al.,J Hepatol, 2016 « DAA and risk for HCC early recurrence : Much ado about nothing » (letter)

- *The 27.6% of recurrence probably relates with different clinical characteristics of pts, different HCC treatment modalities and the wide range of time elapsed between HCC treatment and DAA initiation (1.2 - 87.7 months !)*
- *To evaluate the K-M curve it is statistically correct to use the time of HCC treatment and not the time of DAA initiation : so it will possible the comparison with HCC pts who are cured for HCC but remain viremic*

↓

«…with this statistical correction the 6 and 12 month HCC recurrence rates are 7% and 13%, at variance with reported crude data of 27,6%»

Conti F et al., J Hepatol, 2016 « Early occurrence and recurrence of HCC in HCV-related cirrhosis treated with DAA »

- 344 cirrhotic pts (59 previous HCC) treated with DAA
- Follow-up period = 24 weeks
- SVR = 91%
- HCC detection in follow-up :

  9/285 (3.16%) in HCC – group

  17/59 (28.8%) in HCC + group

↓

« DAA induced resolution of HCV infection not seems to reduce occurrence or recurrence in cirrhotic pts treated for HCC in the short term »

Nault JC, Colombo M, J Hepatol 2016 " HCC and DAA treatments : controversy after the revolution " (Editorial)

" The different studies bring no strong evidence for an increased risk of HCC occurrence in HCV naïve patients treated by DAA. ***However, the persistent risk of HCC development strongly justifies HCC screening after viral clearance in pts with HCV related cirrhosis "***

« Risk of cirrhosis-related complications in pts with advanced fibrosis following hepatitis C virus eradication»
(Van der Meer AJ, J Hepatol, 2017)

- *1000 pts with SVR*
- *Median follow-up = 5,7 yrs*
- *Cumulative 8-year HCC incidence : 1,8%bridging fibrosis*
  8,7% cirrhosis
- *Clinical disease progression : 4,2% bridging fibrosis*
  15,8% cirrhosis

↓

«Chronic HCV infection should preferably be treated before cirrhosis has developed»

Motoyama H et al. «Stagnation of histopathological improvement is a predictor of HCC development after HCV eradication» PLOS one, March 13, 2018.

- 34 IFN patients with liver biopsy before and after SVR achievement: 11 with HCC, 23 without HCC:

✓ Fibrosis stage (Inuyama classification), area collagen deposition, Cytoglobin immunohistochemistry and α smooth muscle actin (→ activity of hepatic stellate cells) :

→ marked decrease in non-HCC group

→ unchanged in HCC-group

↓

«… stagnation of fibrosis regression is associated with a high risk for HCC after SVR»

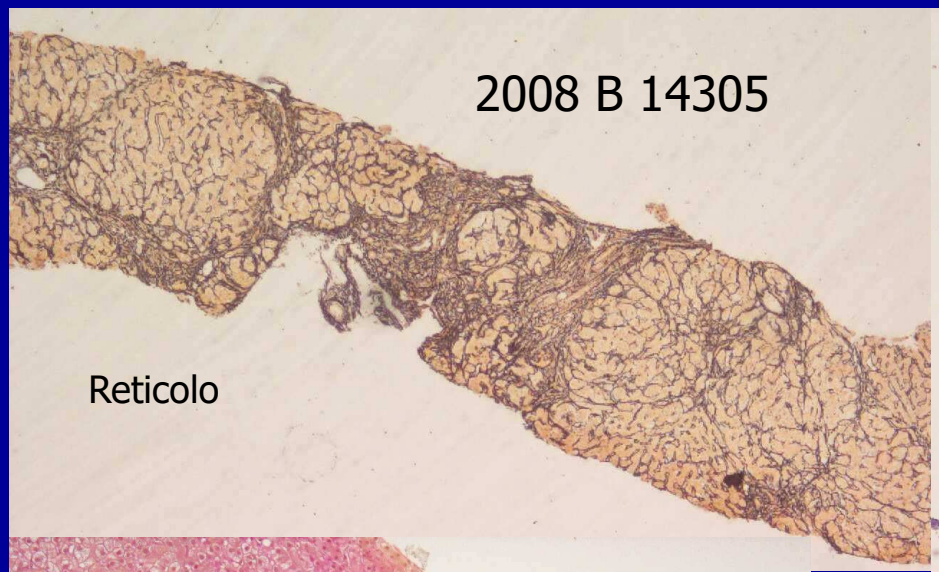
Terapia anti-HCV e «regressione» della fibrosi

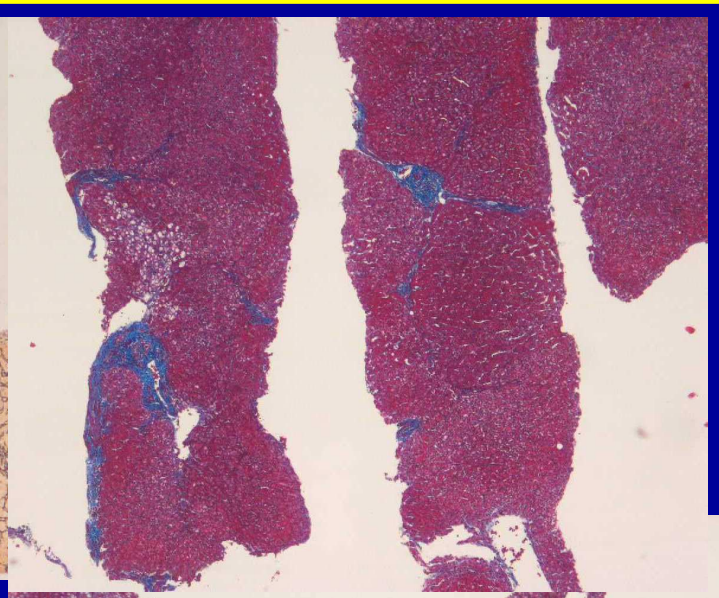
- *Martinez SM et al, "Assessment of liver fibrosis before and after antiviral therapy in chronic hepatitis C", AP&T, 2011.*
- *Ellis EL et al, " Clinical evidence for the regression of liver fibrosis", J Hepatol, 2012.*
- *Poynard T et al, " Slow regression of liver fibrosis ..after virological cure in chronic hepatitis C ", J Hepatol, 2013.*
- *Tachi Y et al., " Liver fibrosis in chronic hepatitis C after the eradication of HCV ", PLOS ONE, July 2015.*

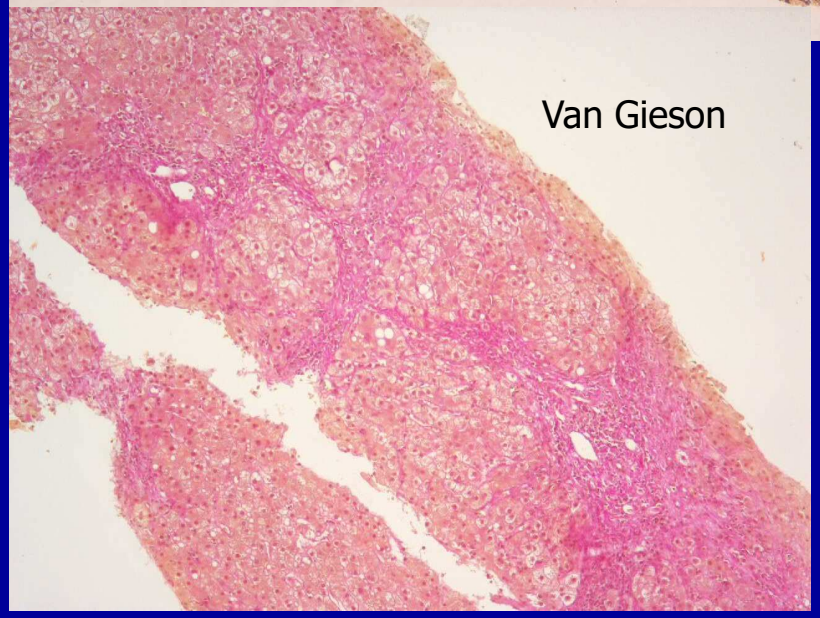
↓

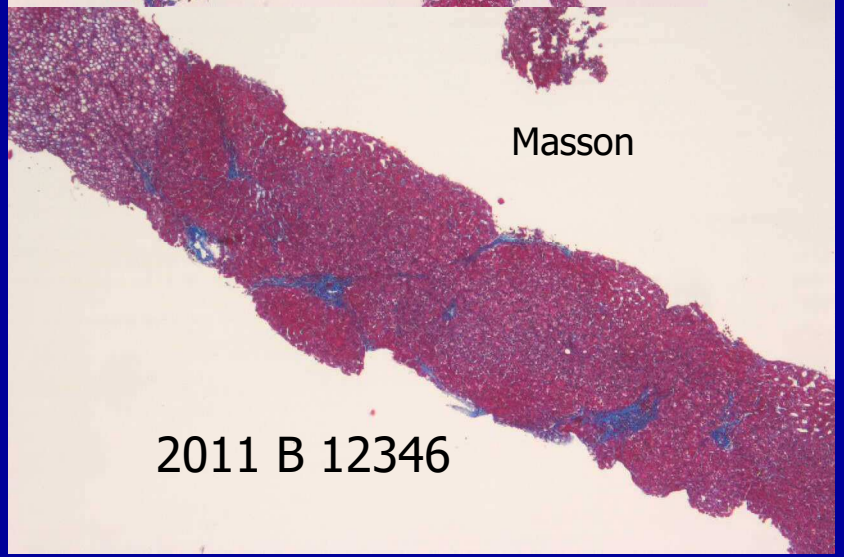
115 pts., pretreatment and 5 years after SVR liver biopsies : lower histological fibrosis grade in the 2° biopsy ($p < 0.0001$); in 5 pts. liver fibrosis progressed (1 diabetes, 3 obesity..)

Reversibilità della Fibrosi









REAL-TIME TISSUE ELASTOGRAPHY

Transient elastography (Fibroscan®)

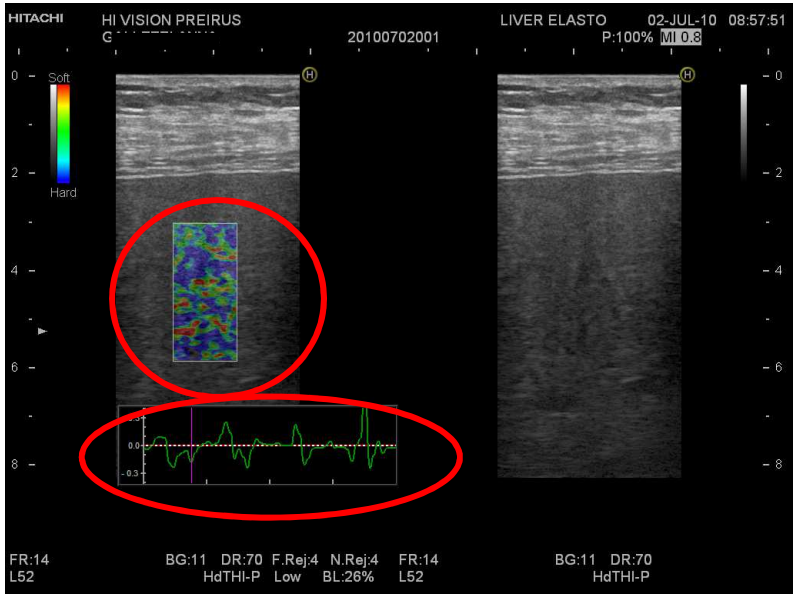
detects the propagation speed of a shear wave transmitted from a probe through the liver and calculates the shear modulus of the liver to evaluate the degree of liver fibrosis. The result is based on *1-dimensional information only.*

(Sandrin L et al. Ultrasound Med Biol. 2003)
(Foucher J et al. Gut 2006)
(Fraquelli M et al. Gut. 2007)
(Abenavoli L,Rapaccini GL,Int J Clin Pract. 2008)
(Berzigotti et al. J Hepatol, 2010)

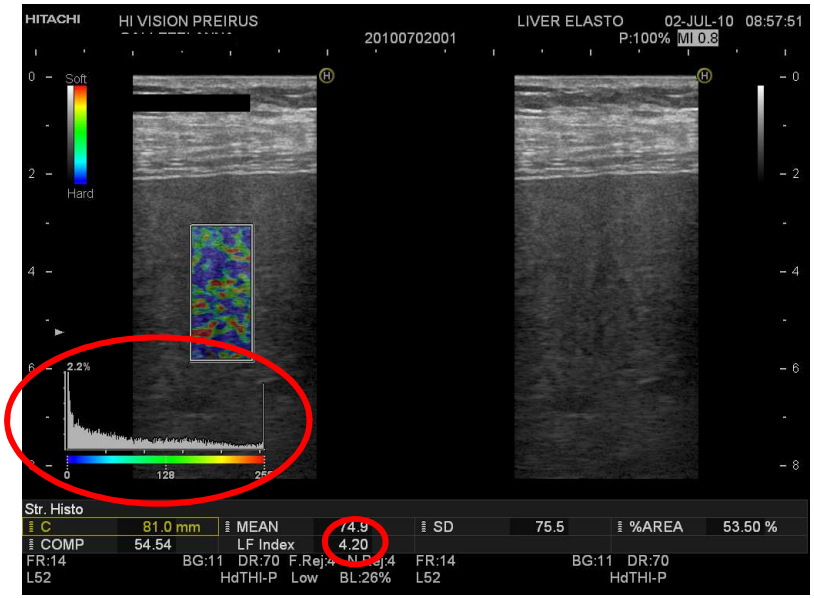
Real time tissue elastography (RTE)

visualizes a *2-dimensional strain image* induced by external freehand compression with the probe or by internal heartbeats. To evaluate the degree of liver fibrosis, it is reported that the pattern of strain image induced by compression becomes patchy *as fibrosis progresses.*

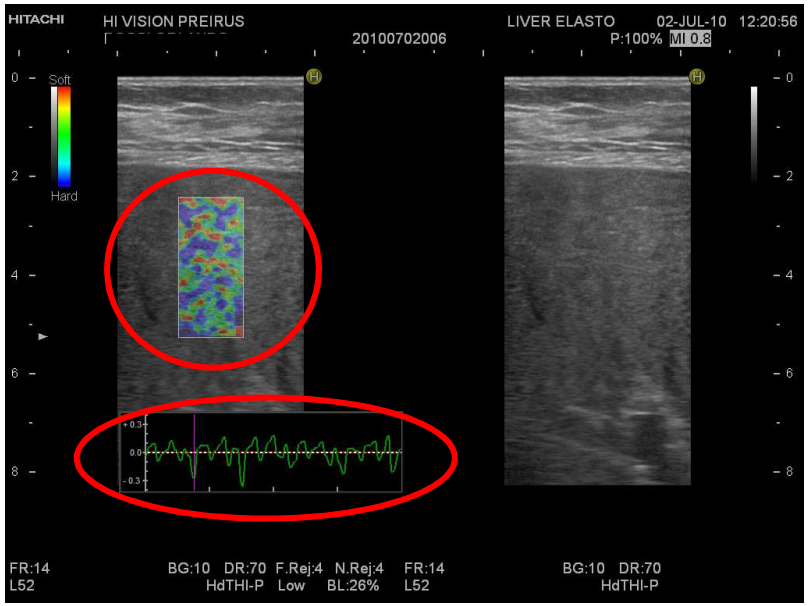
(Fujimoto K et al. Gut. 2007)

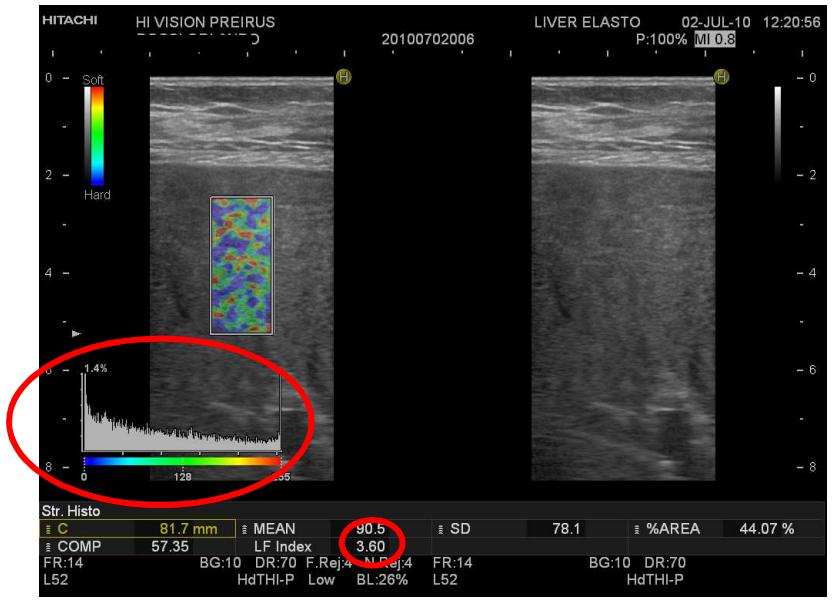


Cirrosi HCV relata



Liver fibrosis index: 4.20





Liver fibrosis index: 3.60

Elastografia nelle Malattie Croniche di Fegato

- Static or Quasistatic Strain Imaging
- One-dimensional Transient Elastography
- Point Shear Wave Elastography
- Supersonic Shear-Wave Elastography
- *MR Elastography*

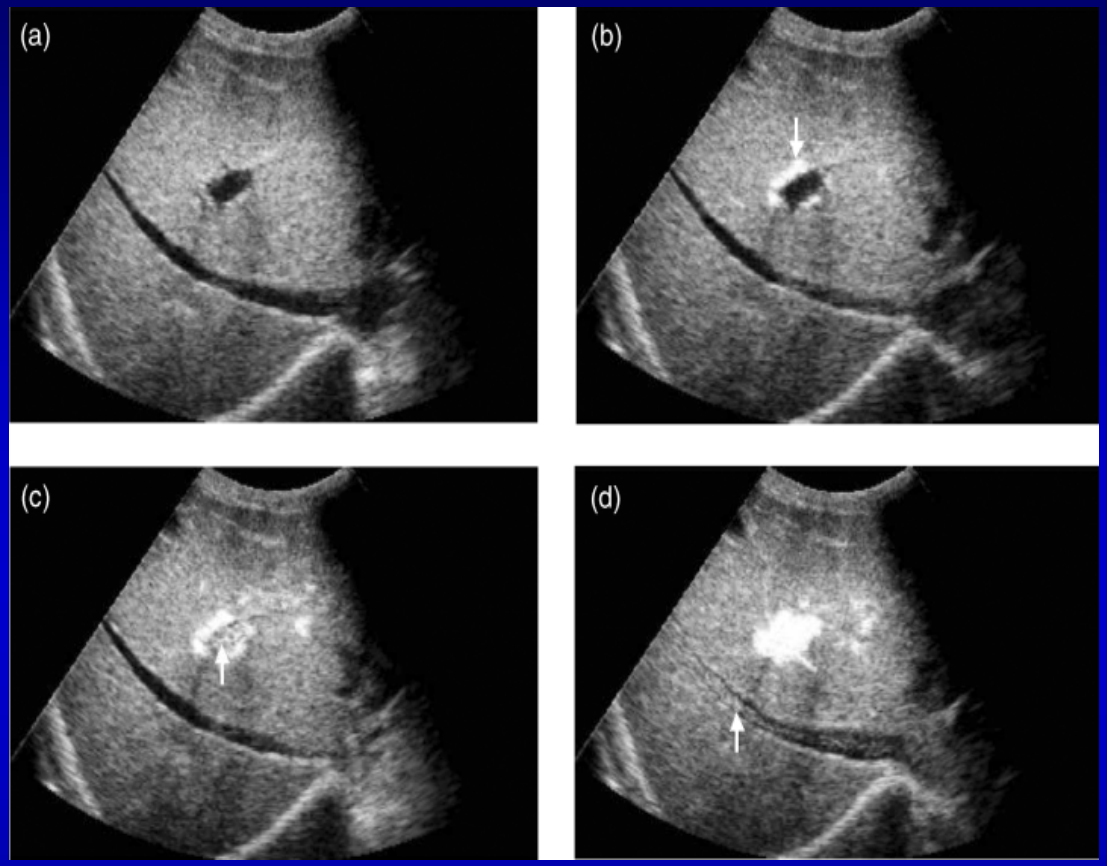
↓

«..elastography has added utility in the follow-up of previously diagnosed fibrosis, the assessment of treatment response, evaluation of portal hypertension (spleen elastography) and evaluation of patients with unexplained portal hypertension»

(Srinivasa B, RadioGraphics, 2016)

A typical example of pulse-inversion imaging

Hirota et al., Liver International, 2005



Just after a bolus injection of Levovist, a right-sided hepatic artery (HA), portal vein (PV), and right hepatic vein (RHV) were simultaneously scanned in a transverse section (a). First, the HA (arrow) was markedly enhanced after 15 s (b), then the PV (arrow) after 18 s (c), and finally, the RHV (arrow) after 37 s (d).

«Liver fibrosis staging with CEUS: prospective multicenter study compared with METAVIR score» Staub F et al. Eur Radiol, 2009

- *METAVIR assessed by biopsy in 99 patients*

↓

✓ *No or moderate fibrosis*

✓ *Severe fibrosis or cirrhosis*

- *With a cut off of 13 sec diagnosis of F3, F4 : Sens = 79%*

Spec = 78,5%

PPV = 78%

NPV = 83,3%

Acc = 79%

«Hepatic Vein Arrival Time as assessed by CEUS is useful for the assessment of portal hypertension in compensated cirrhosis» Kim MY et al., Hepatology, 2012

- *Comparison of HVPG and HVAT in 71 compensated cirrhotics*

↓

There was a statistically significant negative correlation HVAT↔HVPG

- *HVAT cut-off value > 14 sec : sensitivity = 92,7%*
  specificity = 86,7%
  PPV = 90,5%
  NPV = 89,7%
  positive likelihood ratio = 6,96
  negative ″ ″ = 0.08

↓

«HVAT was associated with worse CPT score (P< 0.001) and esophageal varices (P = 0.018).

«Diagnostic accuracy of HVAT performed with CEUS for cirrhosis : a systematic review and meta-analysis» KimG et al.,Gut Liver,2017.

- *Comparison CEUS vs liver biopsy*
- *Methods : QUDAS-II (quality assessment of diagnostic accuracy studies-II) and meta-analysis*

↓

12 studies including 844 patients

↓

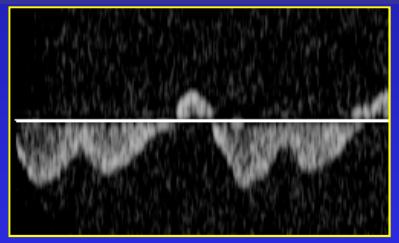
Sensitivity = 83%

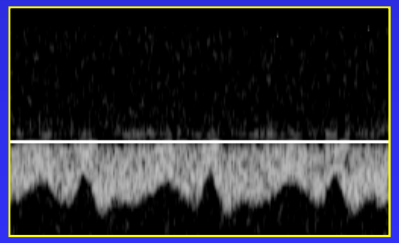
Specificity = 75%

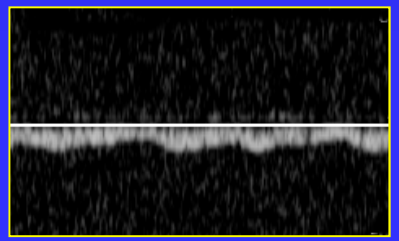
Positive likelihood ratio = 3.45

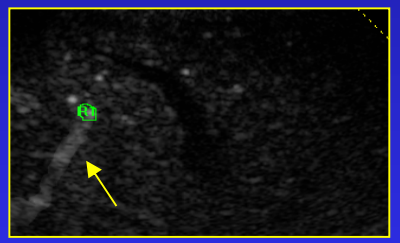
Negative likelihood ratio = 0.28

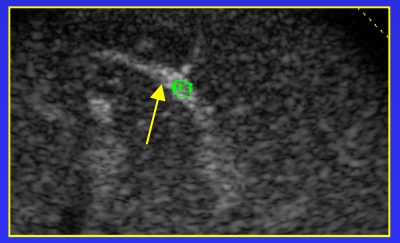
METHODS:We enrolled 26 participants who gave their informed consent: 22 cirrhotics and 4 healthy controls. Doppler shifts signals were obtained from right hepatic vein, using an intercostal scan during end - expiration breath holding**. *To characterize hepatic vein pattern we used an hepatic vein waveform index (HVWI), raising with increasing pulsatility of the waveform. This index is calculated as max vel – min vel / max vel and becomes >1 with the appareance of the triphasic waveform* (*Fig. 1*)**. We recorded out a clip from 20s before to 2min after a peripheral intravenous bolus injection of 2.4ml of SonoVue® (Bracco, Milan). Transit time analysis was perfomed and analysed by a quantification software package. ***We traced the region of interest (ROI) on a branch of hepatic artery, portal and hepatic vein, simultaneously scanned in an intercostal section (Fig 2). The arrival time in the three vessels was defined as the interval from the time of injection and the point of the curve with a signal intensity that exceeds baseline intensity by 10 % and followed by a clear further rise (Fig. 3).*** The time employed by USCA to cross liver from hepatic artery and portal vein to hepatic vein was defined as HA-HVTT and PV-HVTT.

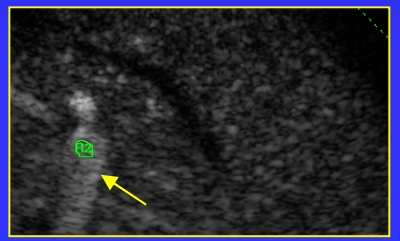


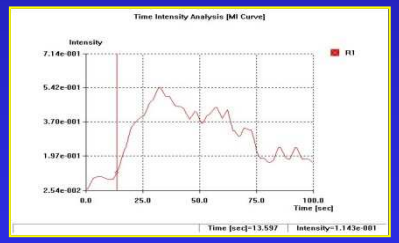


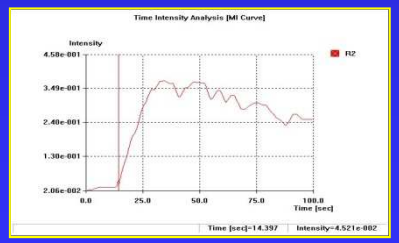


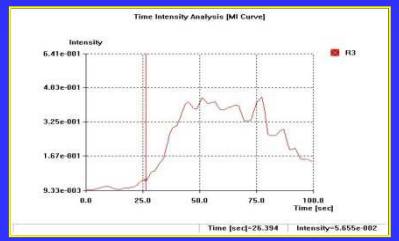












Conclusions

✓ Abnormal hepatic vein Doppler waveform in cirrhotic patients could be due to intrahepatic shunts rather than to lack of liver compliance.

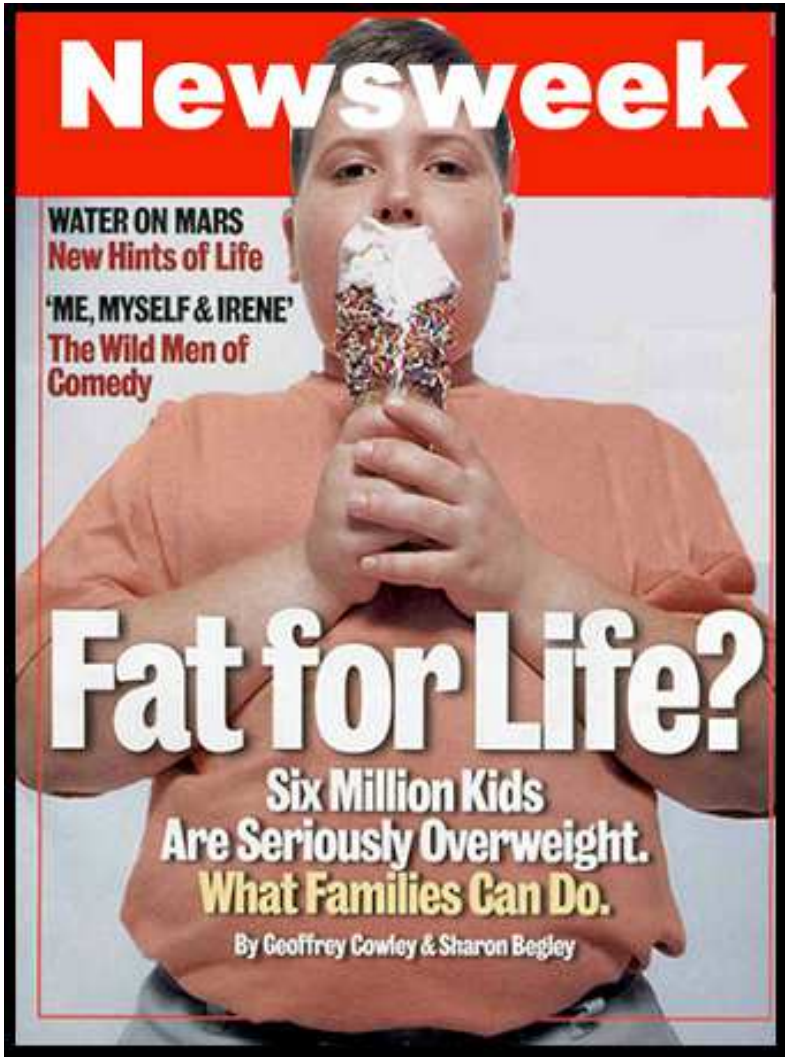
✓HVTT could be useful in the non invasive evaluation of portal hypertension.

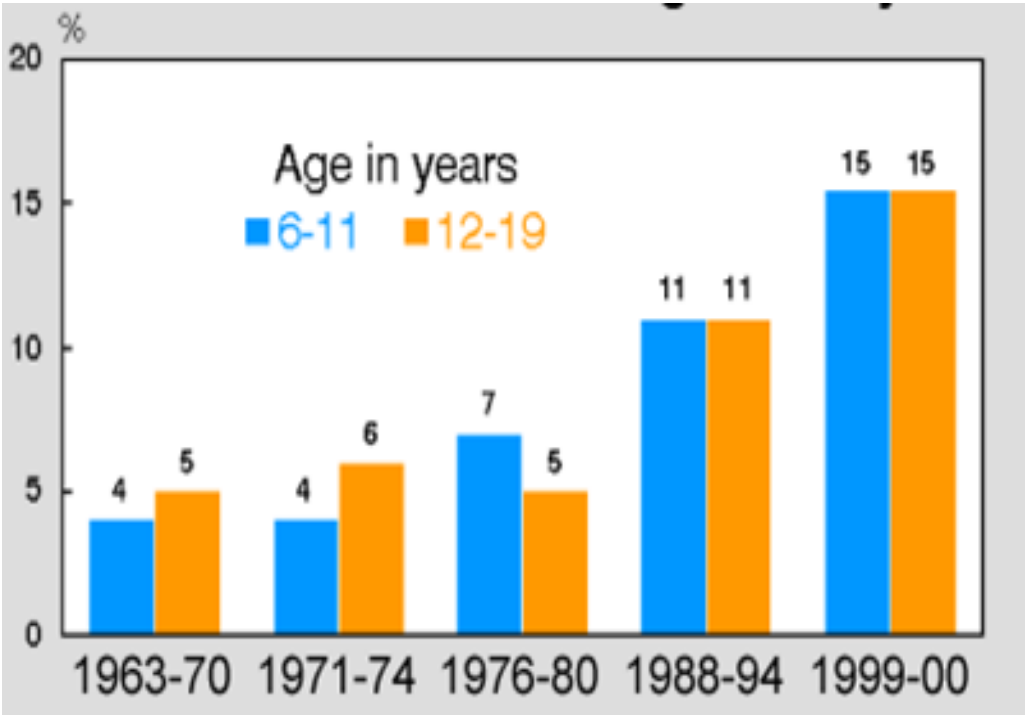
(Siciliani L, Rapaccini GL, J Ultrasound, march 2017)

« Sorveglianza dei pazienti a rischio di HCC »

- Pazienti SVR senza cirrosi : follow-up clinico e virologico ?!?
- Pazienti SVR con cirrosi : follow-up invariato (eco + αFP)
- Pazienti SVR con cirrosi con miglioramento della funzionalità epatica e «regressione» della cirrosi : follow-up invariato per ora….
- Pazienti SVR con cirrosi e deterioramento della funzionalità epatica : sospettare OCI
- Pazienti trattati per HCC con SVR : follow-up più stretto (in caso di nuovi trattamenti dopo resezione/ablazione di HCC consigliabile dilazionare l'inizio del trattamento con nuovo check di HCC : dilazionare di quanto?)

Prevalence of overweight among children and adolescents ages 6-19 in US





Ogden CL et al., JAMA 2002.

Sindrome metabolica

- ***Obesità addominale***

- ***Dislipidemia aterogenica (basso col.-HDL, ipertrigliceridemia)***

- ***Pressione arteriosa elevata***

- ***Insulino-resistenza (con/senza intolleranza al glucosio)***

-Non Alcoholic Fatty Liver Disease

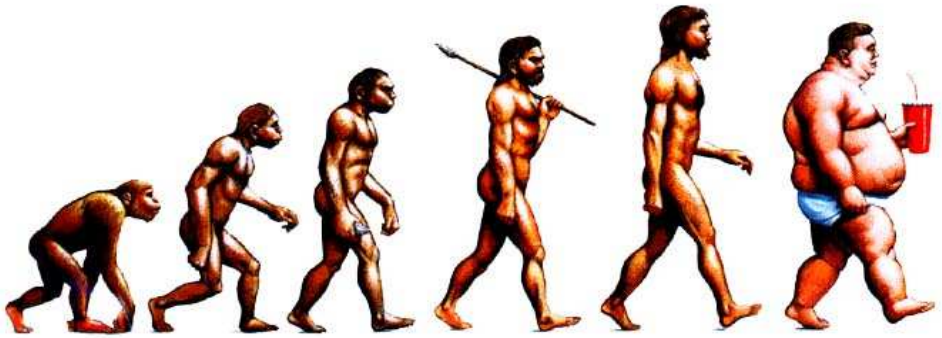
- ***Stato protrombotico***

OBESITA' e TUMORI

- Mammella
- Rene
- Endometrio
- Esofago
- Colecisti
- Colon-retto
- Pancreas
- Tumori ematologici
- Carcinoma epatocellulare
- Carcinoma colangiocellulare (?)

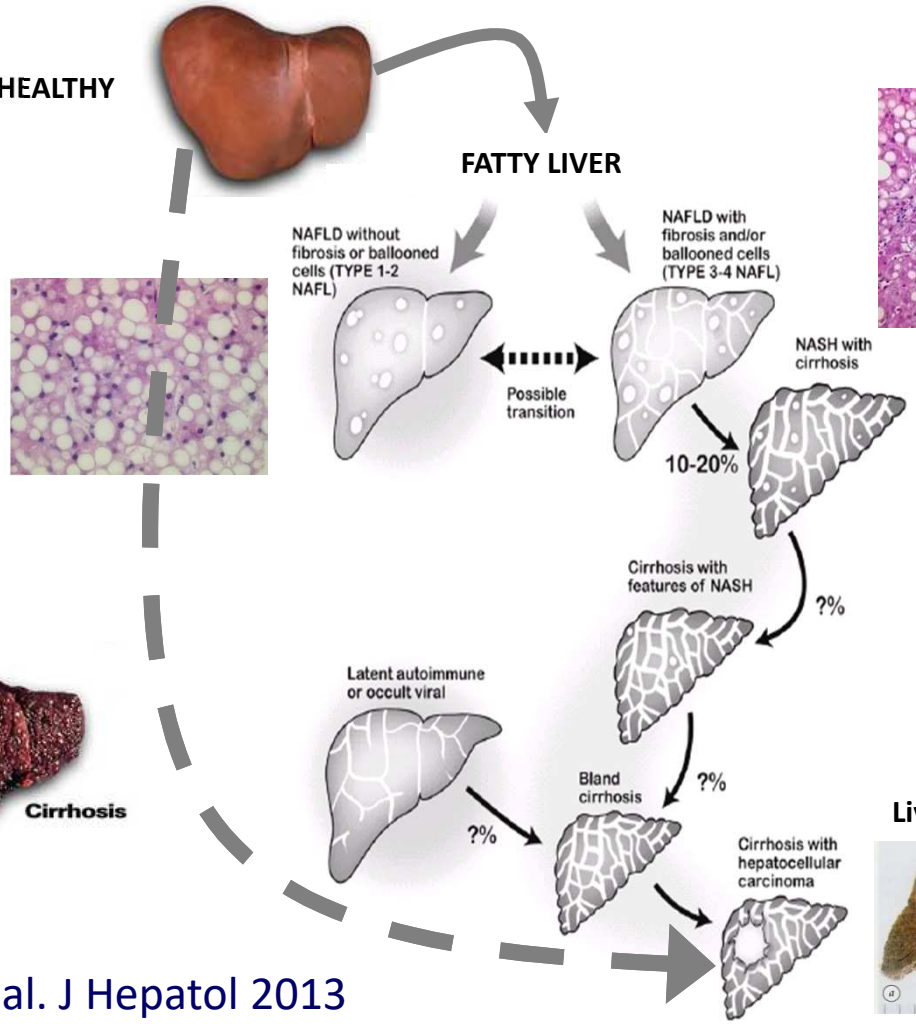
NAFLD

1st cause of CLD in US

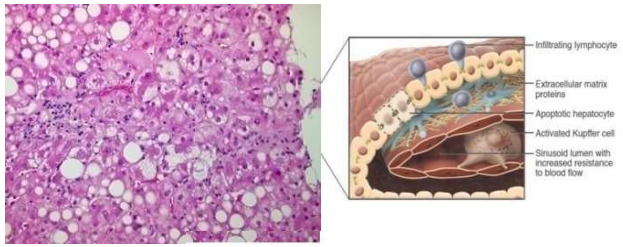


NAFL

- 5.5-30% adults (general pop. NANHES III, Dallas Heart Study, Dyonisos)
- 70% diabetics
- 80% obese
- 13% children (autopsy)
- 38% ob. children



NASH



NASH

- 2,7% adults
- 3% children
- 20% obese
- 25% diabetics

Liver Cancer (HCC)

HCC Incidence

- 0.2-0.7/year

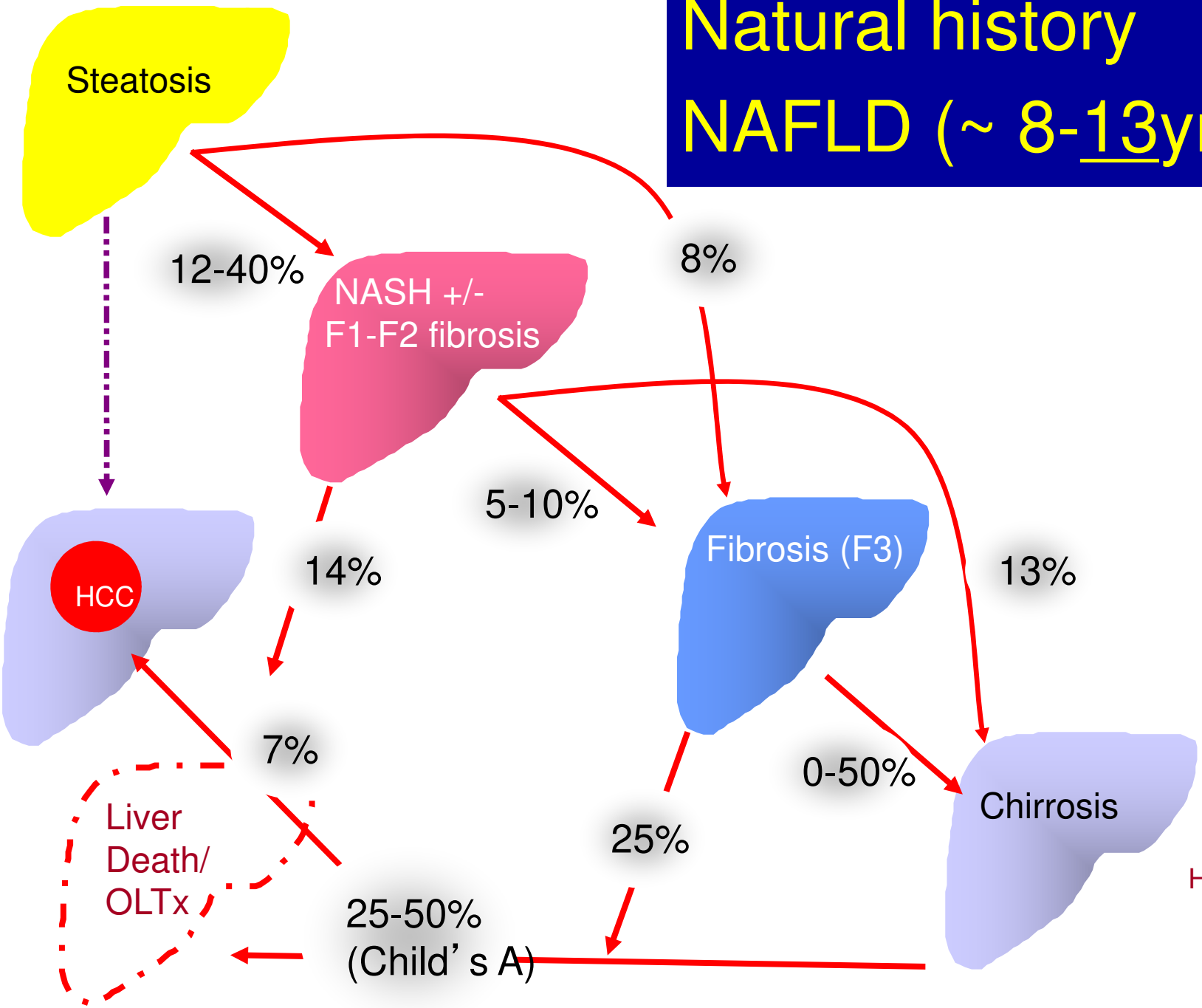
Nobili V, Miele L et al. J Hepatol 2013

Obesità ed Epatocarcinoma (WHO, 2017)

- 650 milioni > 18 anni (13% della popolazione mondiale)
- 340 milioni sovrappeso 5-19 anni
- Il sovrappeso in adolescenza è premessa dell'obesità in età adulta
- Patologie relate all'obesità : m. cardio-vascolari
  diabete tipo 2
  neoplasie
- L'obesità aumenta la mortalità di per sé e nei pazienti trattati per le precedenti patologie

(Saitta C et al., Ann Hepatol, 2019)

Natural history NAFLD (~ 8-13yrs)



Ratzui 2002
Harrison 2003
Fassio 2004
Adams 2005
Sanyal 2006
Ekstedt 2006

Obesity → NAFLD → NASH → Cirrhosis → HCC

- Super-rischio : infezione virale , alcol !
- Il 50% degli HCC associati a NASH sorgono in fegati non cirrotici!

  (Piscaglia F, Hepatology, 2016)
- Su 5000 pts con HCC, quelli associati a NAFLD hanno avuto una peggior OS ed una maggior mortalità tumore-relata rispetto a quelli associati ad altra eziologia

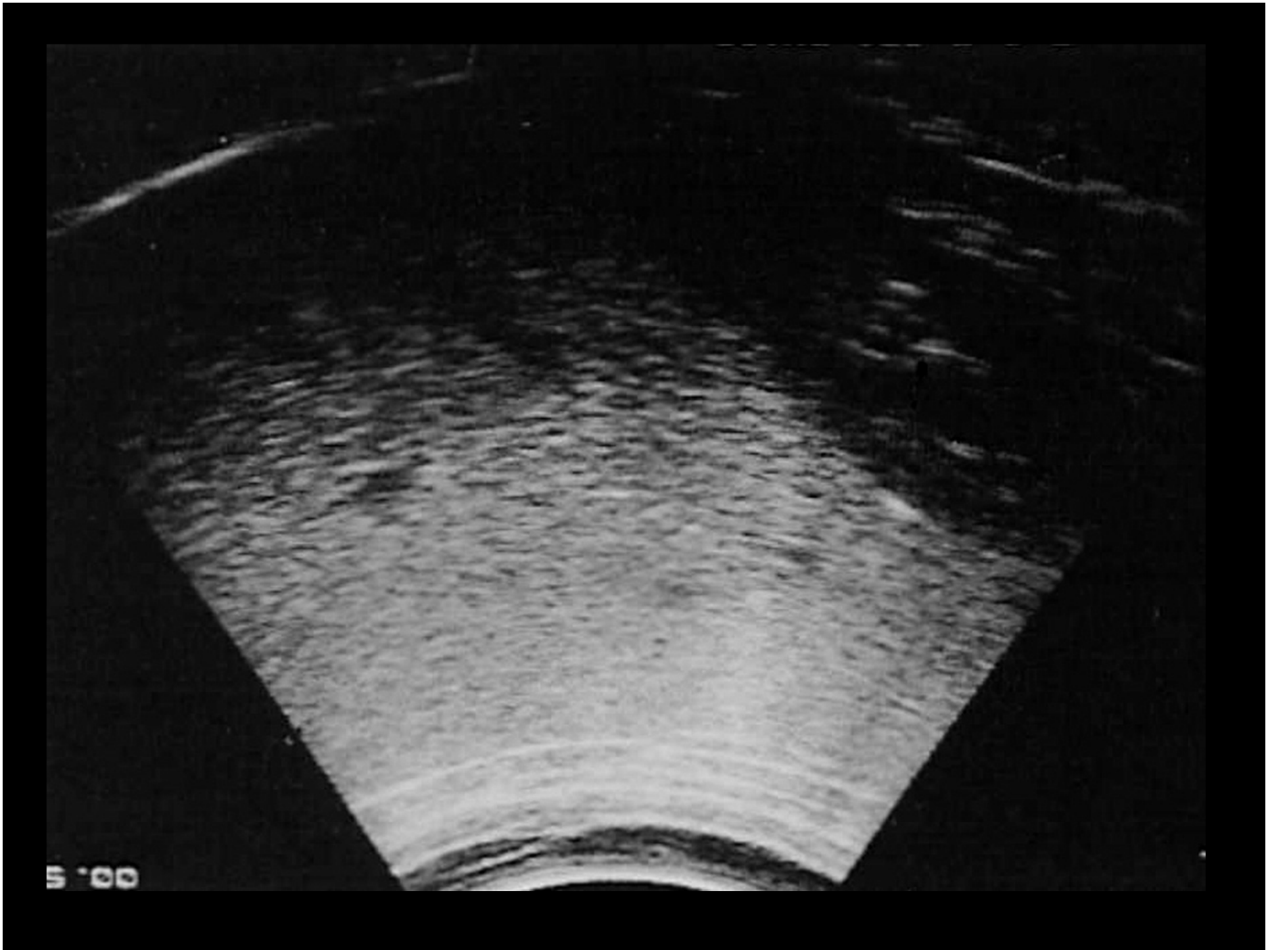
  (Younossi ZM , Hepatology, 2015)
- Non aderenza a programmi di sorveglianza per HCC :

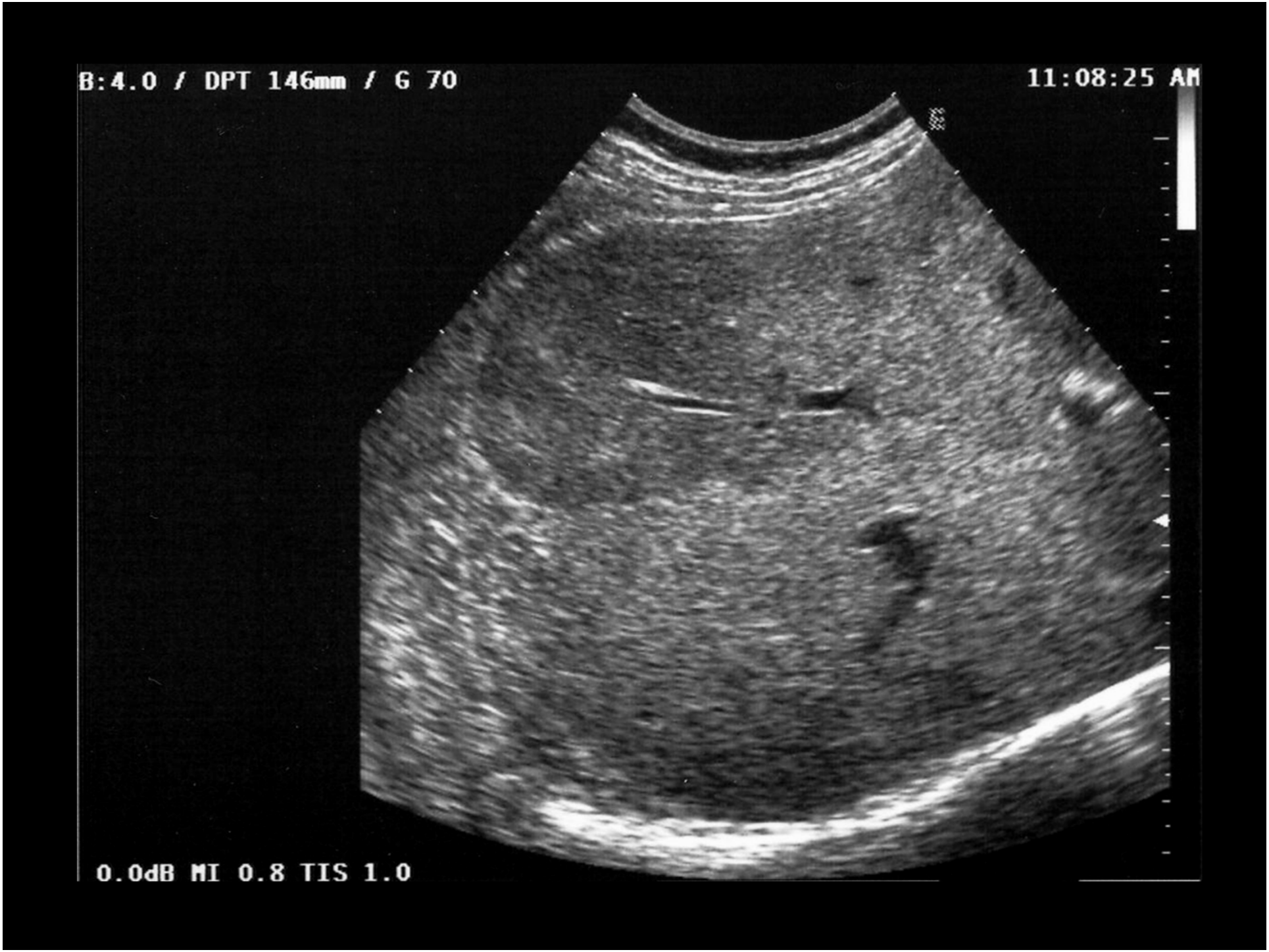
  NAFLD/HCC = 56,7% ; Alcol/HCC = 40,2% ; Virus/HCC = 13,3%

  (Mittal S, Clin Gastr Hepatol, 2015)

↓

Esame di imaging per effettuare la sorveglianza ?!?


5 '00


B:4.0 / DPT 146mm / G 70
11:08:25 AM
0.0dB MI 0.8 TIS 1.0

Come effettuare la sorveglianza nell'obesità con malattia cronica di fegato ?

- 1/3 dei cirrotici con BMI > 35 hanno un esame ecografico non adeguato

  (*Simmons O, Alim Pharmacol Ther, 2017)*

- TC o RM nella popolazione con BMI > 35 non è cost-effective

↓

Stratificare la popolazione NAFLD/NASH/cirrosi ed effettuara la sorveglianza solo nella cirrosi ?

↓

Come stratificare la popolazione ? Test non invasivi di fibrosi ? Elastografia ? Biopsia epatica ?

Possibili interventi per ridurre il rischio di HCC negli obesi con malattia cronica di fegato

- *FATTORI DIETETICI :*

✓ *una dieta ricca di frutta e vegetali riduce il rischio di HCC*

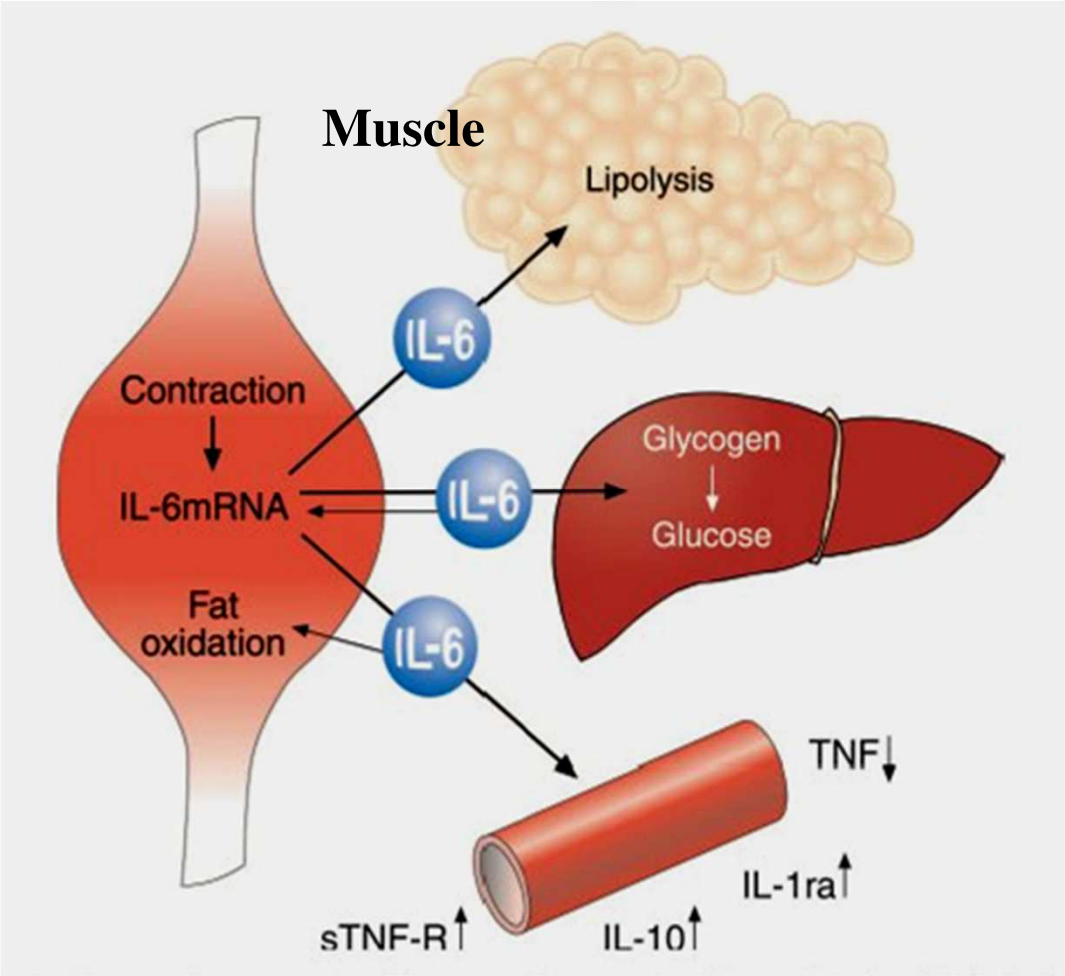
(Saran U, J Hepatol, 2016)

✓ *una forte aderenza alla dieta mediterranea si associa ad una riduzione del 50% dell'incidenza di HCC*

(Turati F, J Hepatol, 2014)

- *ATTIVITA' FISICA : su una popolazione di 500.000 soggetti (NIH study), l'attività fisica continuativa ha ridotto significativamente il rischio di HCC (Beherens G, Eur J Epidemiol, 2013)*
- *METFORMINA (?)*
- *CHIRURGIA BARIATRICA (?)*

Here, we suggest that **myokines** may be involved in mediating the health-beneficial effects of exercise and that these in particular are involved in the protection against chronic diseases associated with low-grade inflammation such as **diabetes and cardiovascular diseases**.



Effetto protettivo dell'esercizio
contro lo stato pro-infiammatorio di diabete, sindrome metabolica, ecc.

Berzigotti A. et al. « Physical activity and liver diseases», Hepatology, Mar 2016

- *L'attività muscolare nel soggetto sano interagisce con il tessuto adiposo, riducendo l'accumulo di grasso nel fegato*
- *L'attivtà muscolare (moderata) nel pz con malattia cronica di fegato, riduce il rischio di encefalopatia epatica*
- *Studi epidemiologici indicano un minor rischio di tumore epatico in pz che svolgono regolare e protratta attività fisica.*
- *L'attività fisica si è dimostrata efficace nel migliorare la qualità di vita nei pz trapiantati di fegato*

Whitsett M et al. « Physical activity as a treatment of NAFLD : a systematic revue» World J Hepatol, 2015 Aug

- *Ruolo dell'esercizio fisico su NAFLD, insulino-resistenza e aterosclerosi*
- *Analisi di 18 studi per complessivi 6925 pazienti*
- *Effetto di esercizio fisico da solo o in combinazione con dieta e modifica di comportamenti di vita.**
- *5 studi hanno verificato l'effetto dell'esercizio fisico mediante ripetute biopsie epatiche per valutare l'effetto sull'istologia del fegato*
- *I parametri esaminati sono migliorati nella popolazione sottoposta alla modifica dei tre parametri presi in considerazione **

Ue, 200 milioni sovrappeso In Italia il record di bambini obesi

di Michela Di Maria

E' allarme obesità nell'Unione Europea. Ogni anno sono 400.000 i bambini in sovrappeso e 200 milioni gli adulti nella stessa situazione. Una vera e propria "epidemia" continentale. Il commissario europeo per i consumatori, Markos Kyprianou, lancia la campagna a favore di corretta alimentazione, salute e attività fisica, osservando come «il nostro continente affronta un fenomeno obesità simile a quello del Nord America».

Preoccupa, in particolare, il dato dell'Italia. L'obesità infantile in 9 anni è passata dal 6,1% al 13,6%. Fortissimi i rischi di diventare adulti "oversize".

Per ridurre il rischio cardiovascolare l'attività fisica e sportiva va iniziata nell'infanzia

..1962..

..2019..

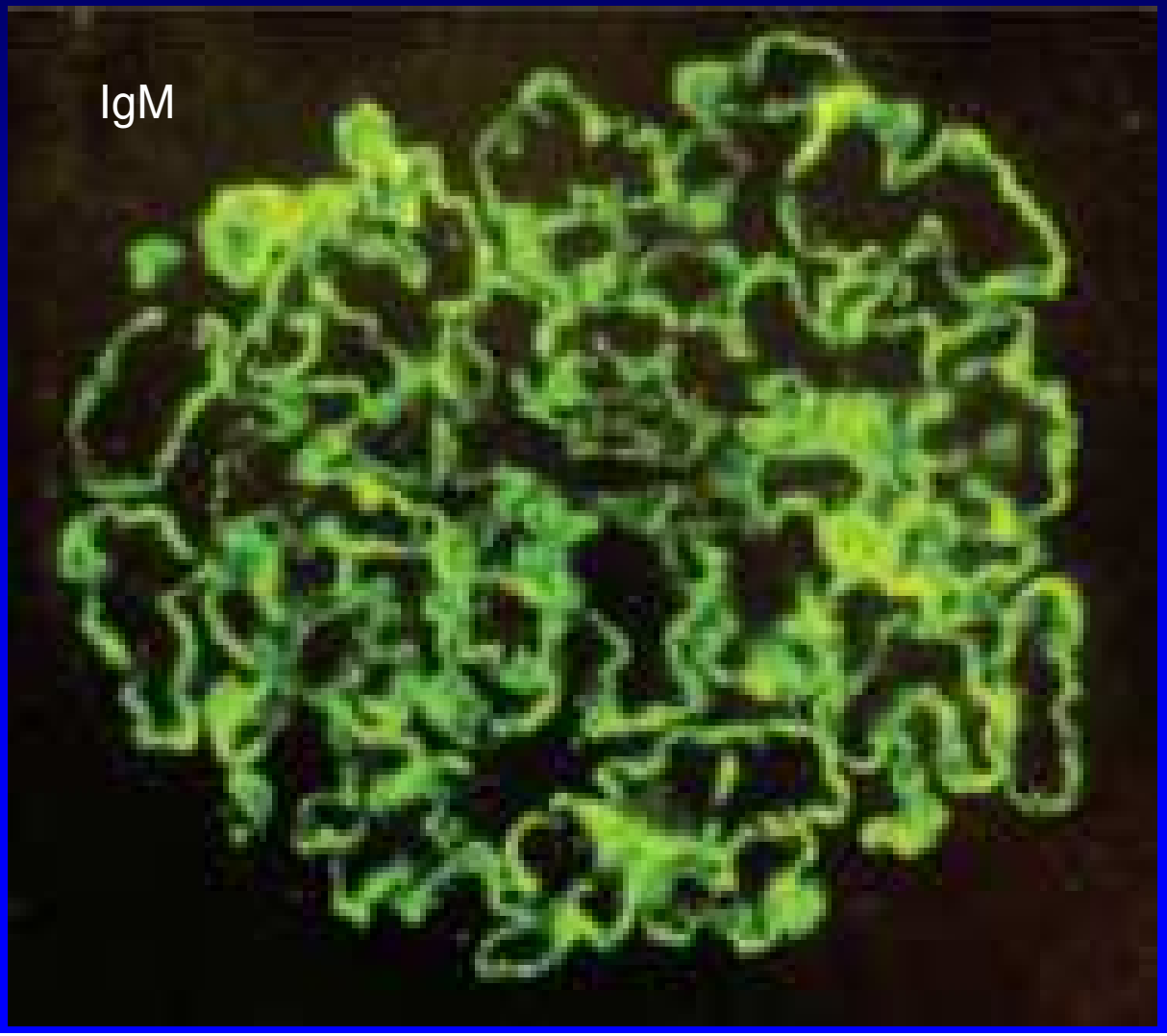
Journal of Ultrasound

www.springer.com/40477

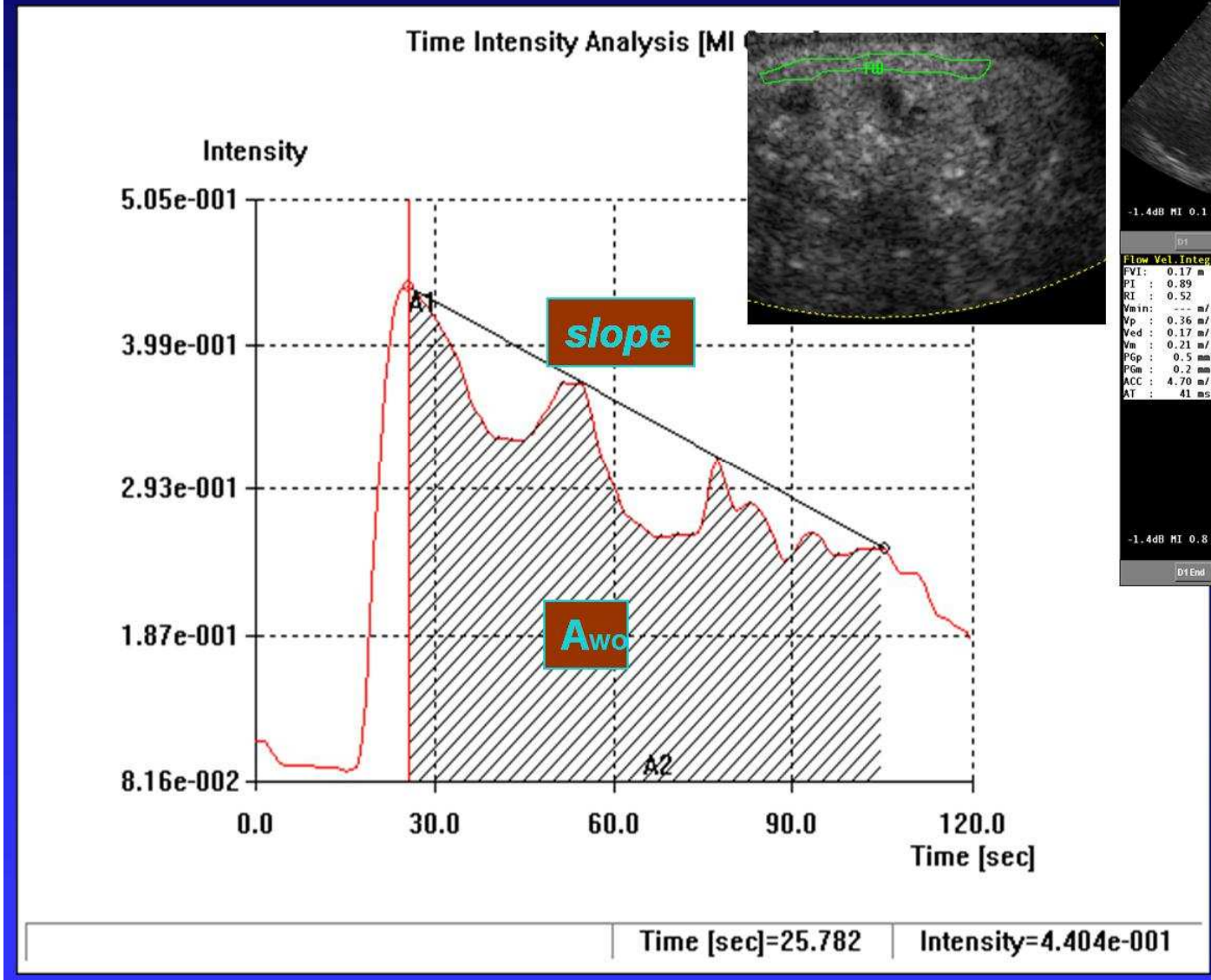
Springer

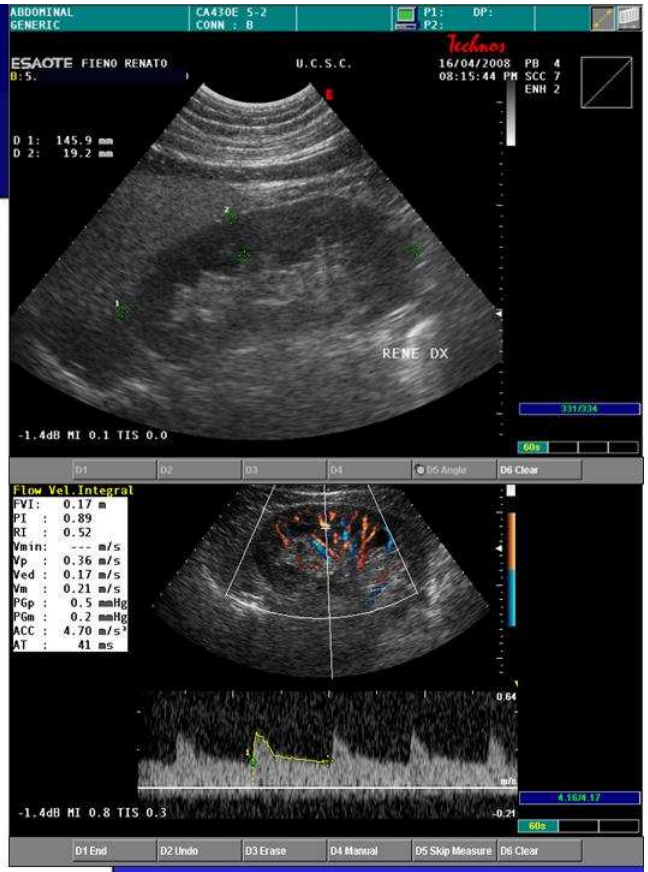
Thank you very much for your kind attention…

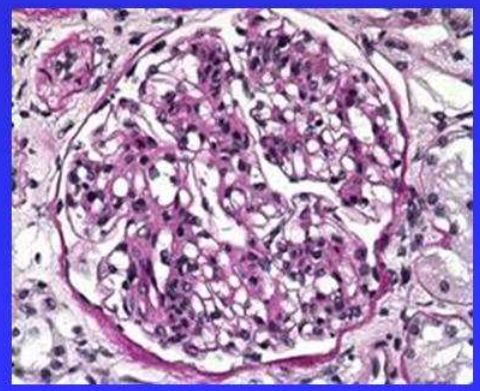
Sansonno et al. Hepatitis C virus RNA and core protein in kidney glomerular and tubular structures isolated with laser capture microdissection. Clinical and Experimental Immunology 2005; 140: 498–506



CASO II





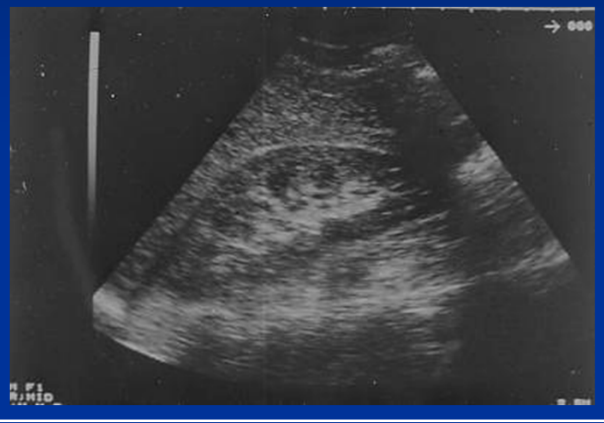


GN da IgA

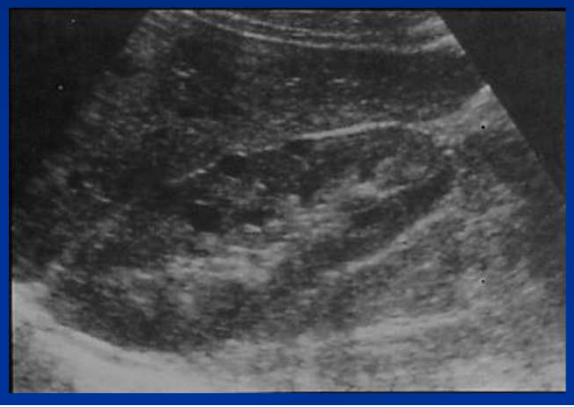
NEFROPATIE MEDICHE CRONICHE: SEGNI ECOGRAFICI

- Incremento ecogenicità corticale

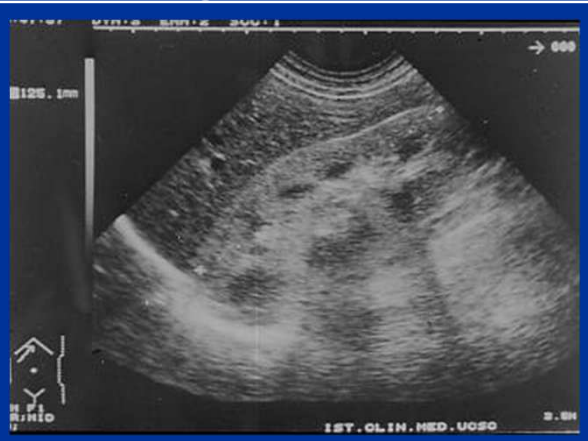
Grado 0: ecogenicità corticale < ecogenicità epatica



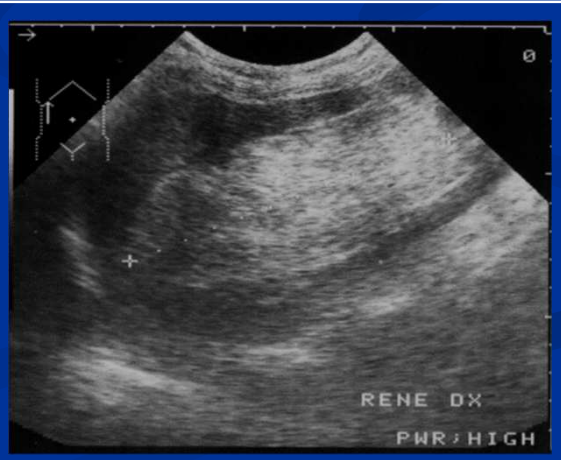
Grado 1: ecogenicità corticale = ecogenicità epatica



Grado 2: ecogenicità corticale > ecogenicità epatica < ecogenicità seno renale



Grado 3: ecogenicità corticale > ecogenicità epatica = ecogenicità seno renale



RESULTS

- SVR12 : 97,5 %
- Median follow-up time after DAA : 5,7 mth
- 3 pts died
- 16 HCC recurrence (27,6%)
- Median time from DAA starting to HCC recurrence: 1,5 mth
- The pattern of recurrence was heterogeneous

$$\rightarrow it\ is\ important\ to\ follow-up\ all\ the\ patients\ enrolled\ to\ DAA\ therapy\ irrespective\ of\ a\ prior\ diagnosis\ of\ HCC$$

ANRS collaborative study group, J Hepatol, 2016

« Lack of evidence of an effect of DAA on the recurrence of HCC»

- *Recurrence of HCC after DAA treatment in three prospective cohorts :*

1. *267 pts previously treated for HCC*
2. *79 pts with incidental HCC*
3. *314 liver transplants recipients for HCC*

↓

“ In three distinct prospective cohorts, it was not observed an increased risk of HCC recurrence, notably in pts who underwent curative HCC treatment, including OLT ”

HCC risk in HCV patients after SVR : variable «fibrosis»

- Kobayashi M et al., J MED Virol, 2016.

  605 DAA or IFN treated patients :

  - Fib-4 score > 3.25 HCC occurrence 4.35 and 3.95 at 3 years

  - Fib-4 score < 3.25 HCC occurrence 0.00 and 0.48 at 3 years

- D'Ambrosio R et al., Liver Int, 2018.

  38 IFN patients : liver biopsy 5 years after SVR :

  Patients who developed or did not an HCC had similar rates of residual cirrhosis, collagen content or steatosis

↓

«..the 8-year cumulative probability of HCC was 17% indipendently on cirrhosis regression»

Populations at risk

- *Intravenous drug users*
- *History of blood products or unsafe injections*
- *Piercings and tattoos*
- *Prisoners*
- *Homeless people*
- *Sexual behaviour at risk*

« Mortality in hepatitis C pts who achieve a SVR compared to the general populations »
(Innes H et al., J Hepatol, 2017)

- *1824 pts*
- *Follow-up = 5,2 yrs after SVR*
- *All-cause mortality : 1,9 more frequent in SVR group (HCC, alcohol use, injecting drug use).*

↓

"individuals without these behavioural markers (32,8% of the cohort) had equivalent survival to the general population !"

« The HCV care continuum does not end with cure : a call to arms for the prevention of reinfection»

(Falade-Nwulia O et al, J Hepatol, 2017)

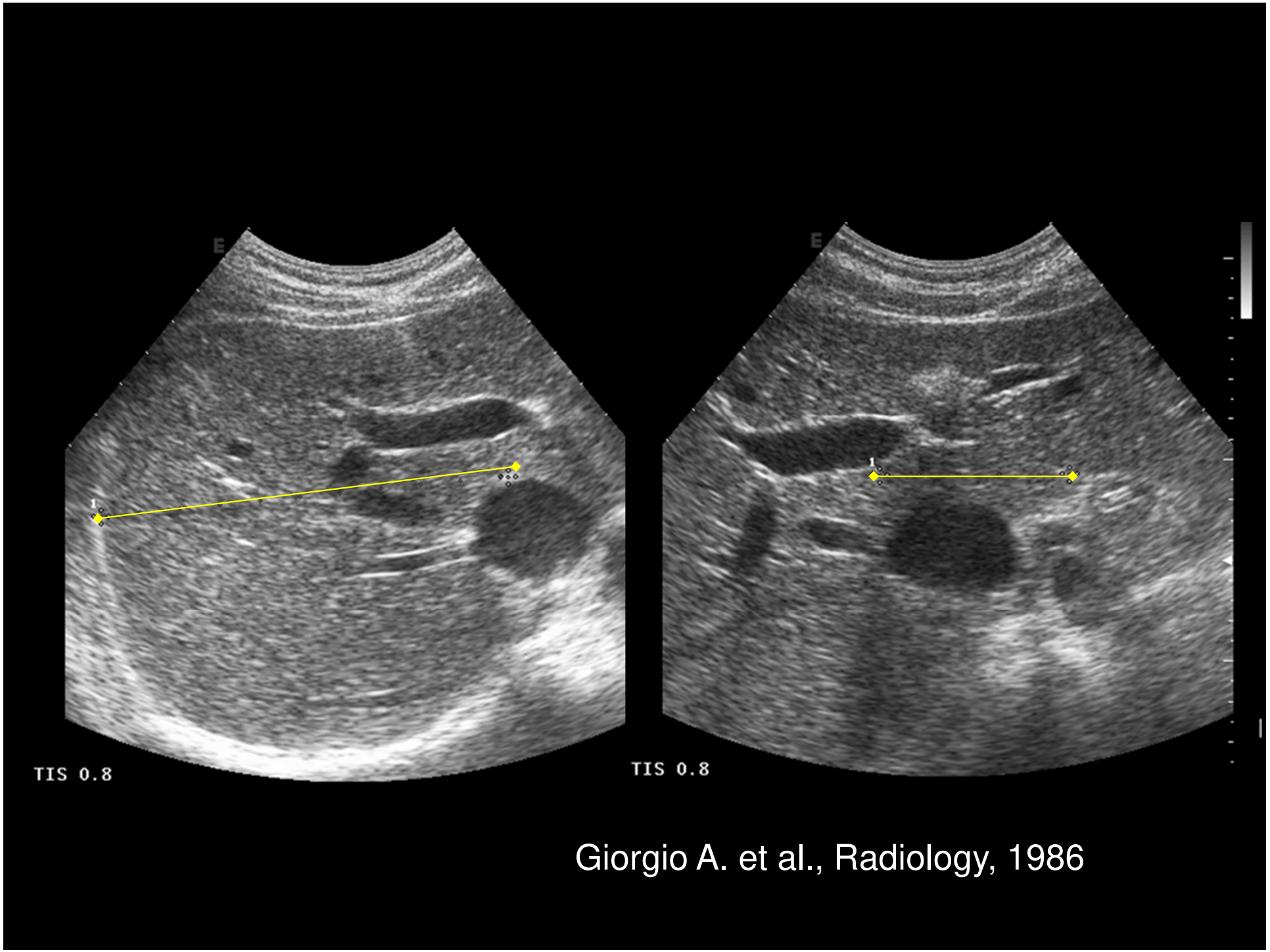
- *The HCV care continuum does not end with cure*
- *The prevention of reinfection must be adressed in people at risk*
- *To date two patient groups at high risk :*
  - *injecting drugs users*
  - *HIV-infected men who have sex with men*
- *After SVR : at least annual HCV RNA testing*

"Field practice study of half-dose sorafenib treatment of safety and efficacy for HCC : a propensity score analysis" (M Morimoto,et al, Hepatol Res, 2014)

- *218 pts. with intermediate or advanced stage : 73 half dose*
  145 full dose
- *Overall survival : half-dose = 10.2 months*
  full-dose = 8.8 months (p = .911)
- *Progression-free survival : half-dose = 3.8*
  full-dose = 2.5 (p = .143)
- *Grade 3-4 adverse effects : half-dose = 47,4 %*
  full-dose = 66.7 % (p = .037)

↓

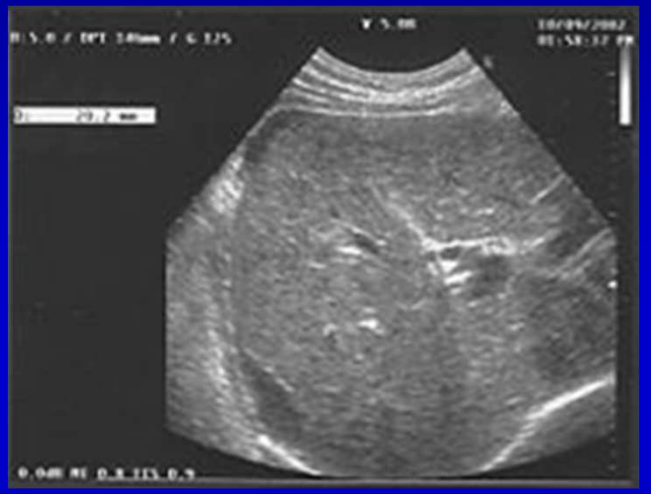
..initial half-dose sorafenib led to fewer severe adverse effects and a comparable survival benefit compared full-dose in patients with HCC, particularly for those of advanced age !

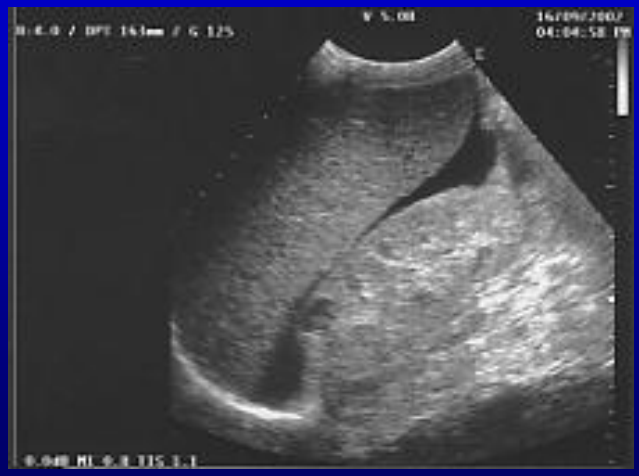


Giorgio A. et al., Radiology, 1986

ASCITE

- L'ecografia è particolarmente utile nella diagnosi dello scompenso ascitico iniziale non ancora clinicamente evidente





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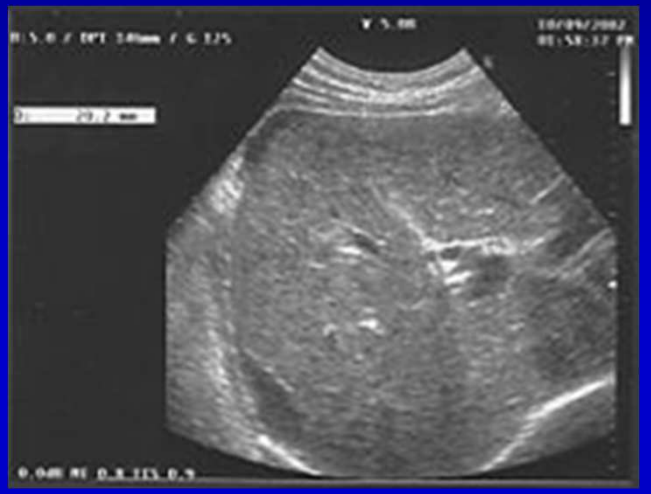
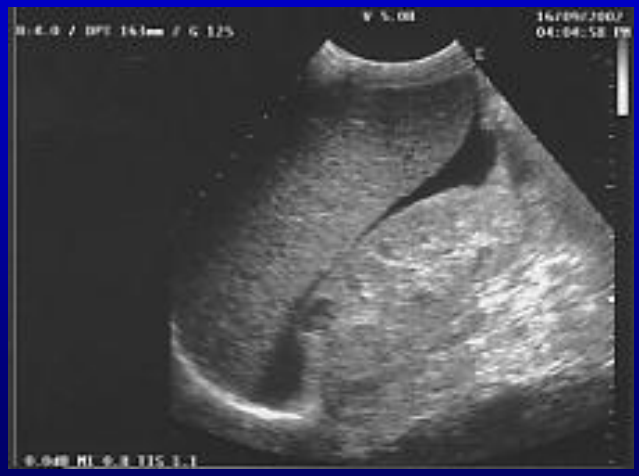
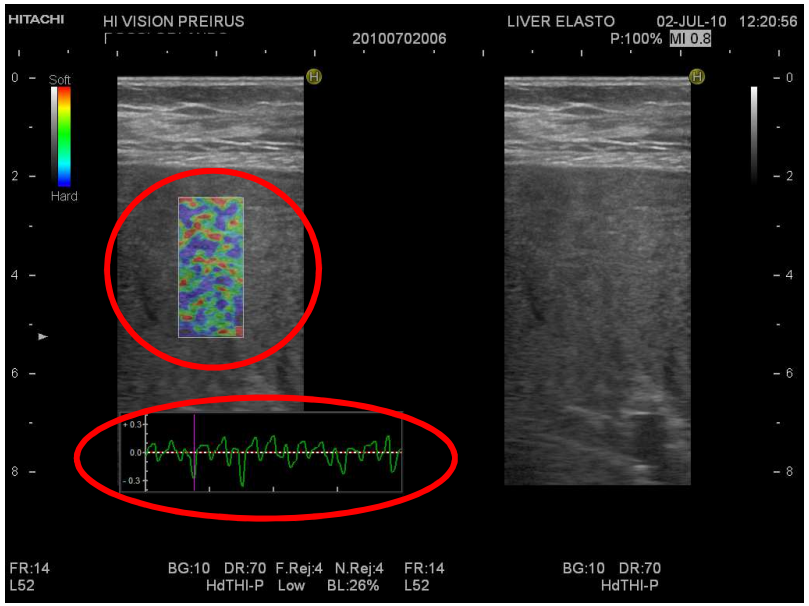
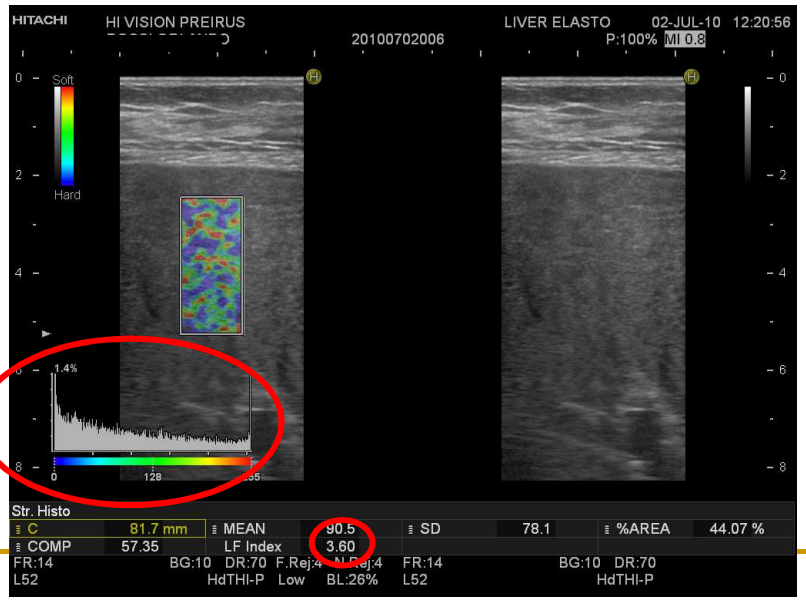


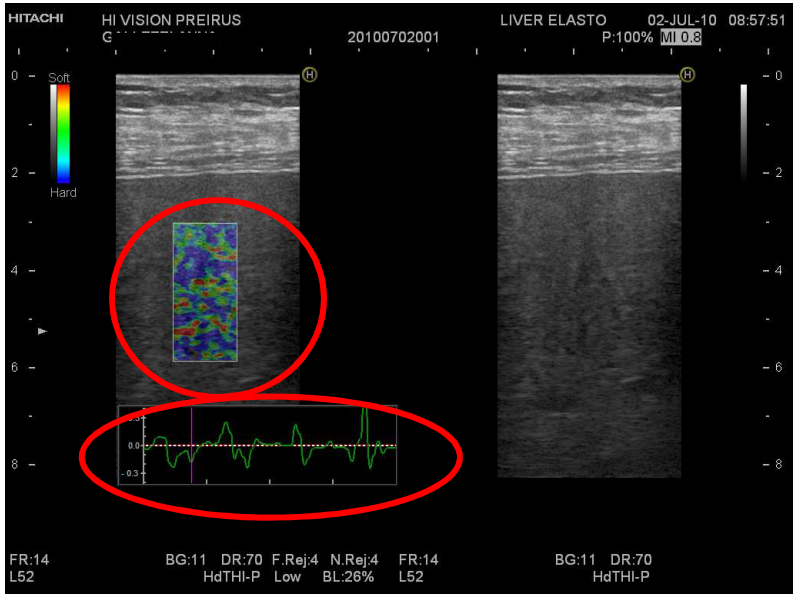




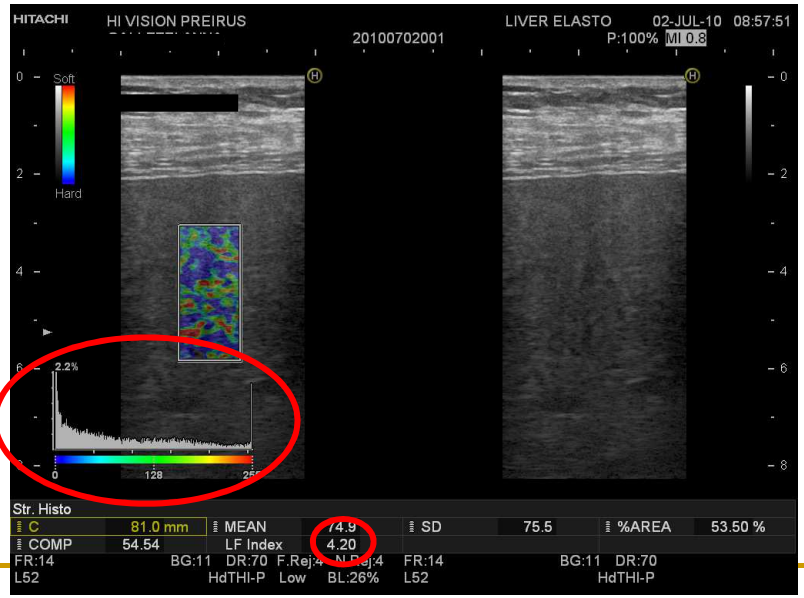
Chronic alcoholic hepatitis



Liver fibrosis index: 3.60

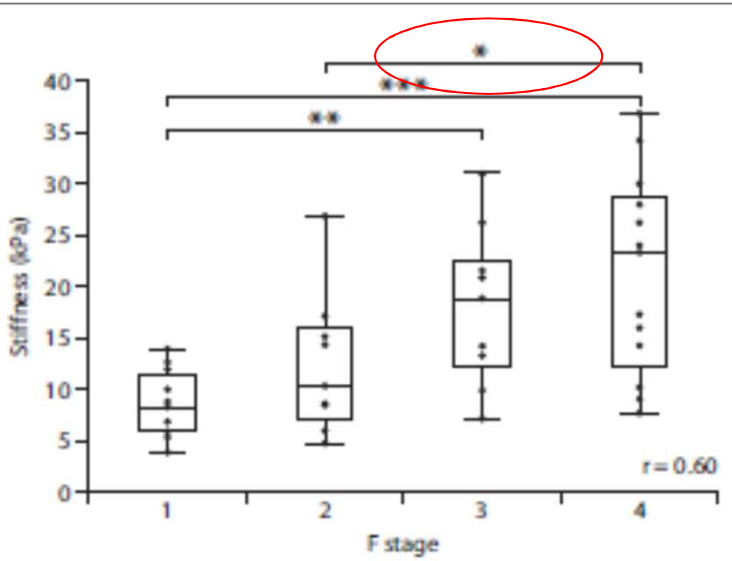


Cirrhosis

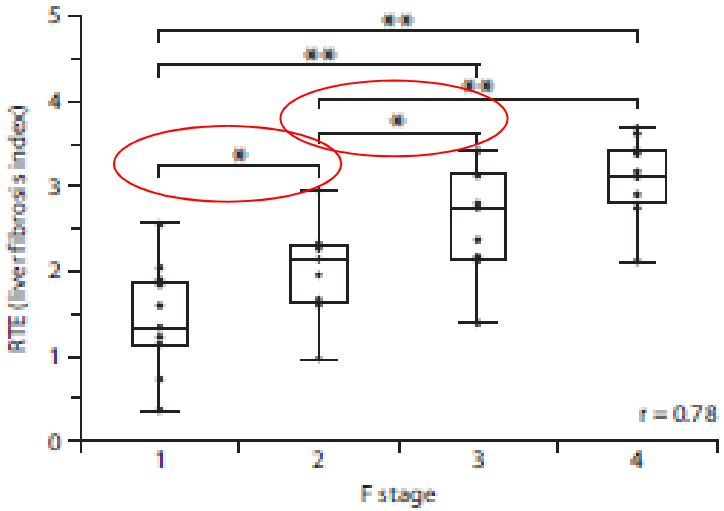


Liver fibrosis index: 4.20

FibroScan and F stage
*** p < 0.05; ** p< 0.005; *** p< 0.001**

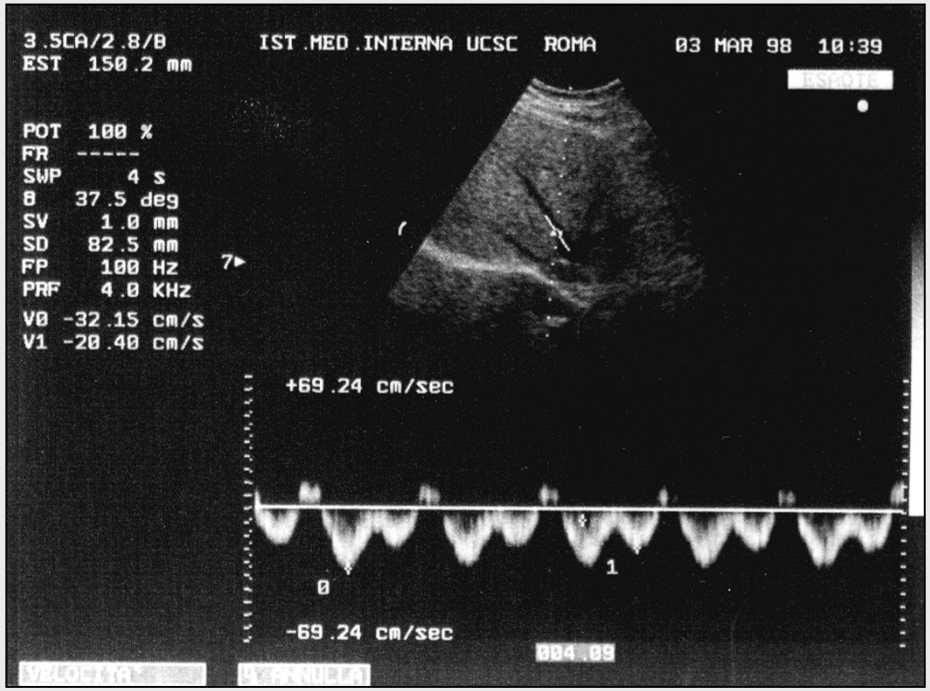


RTE (liver fibrosis index) and F stage
*** p < 0.05; ** p< 0.001**

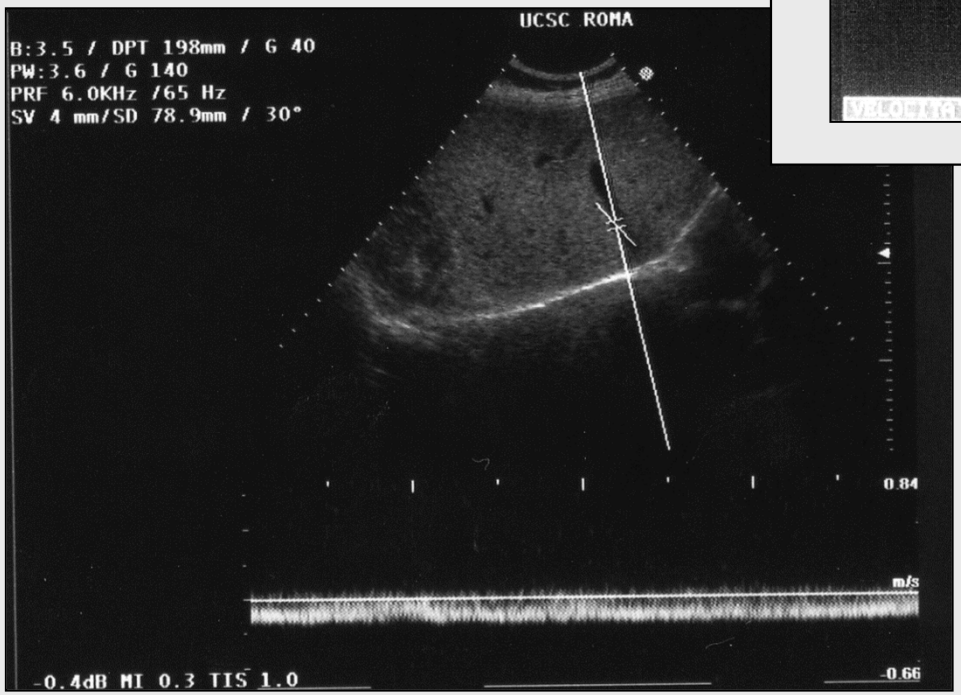


(Tatsumi C et al. Intervirology. 2010)

VENA SOVRAEPATICA MEDIA



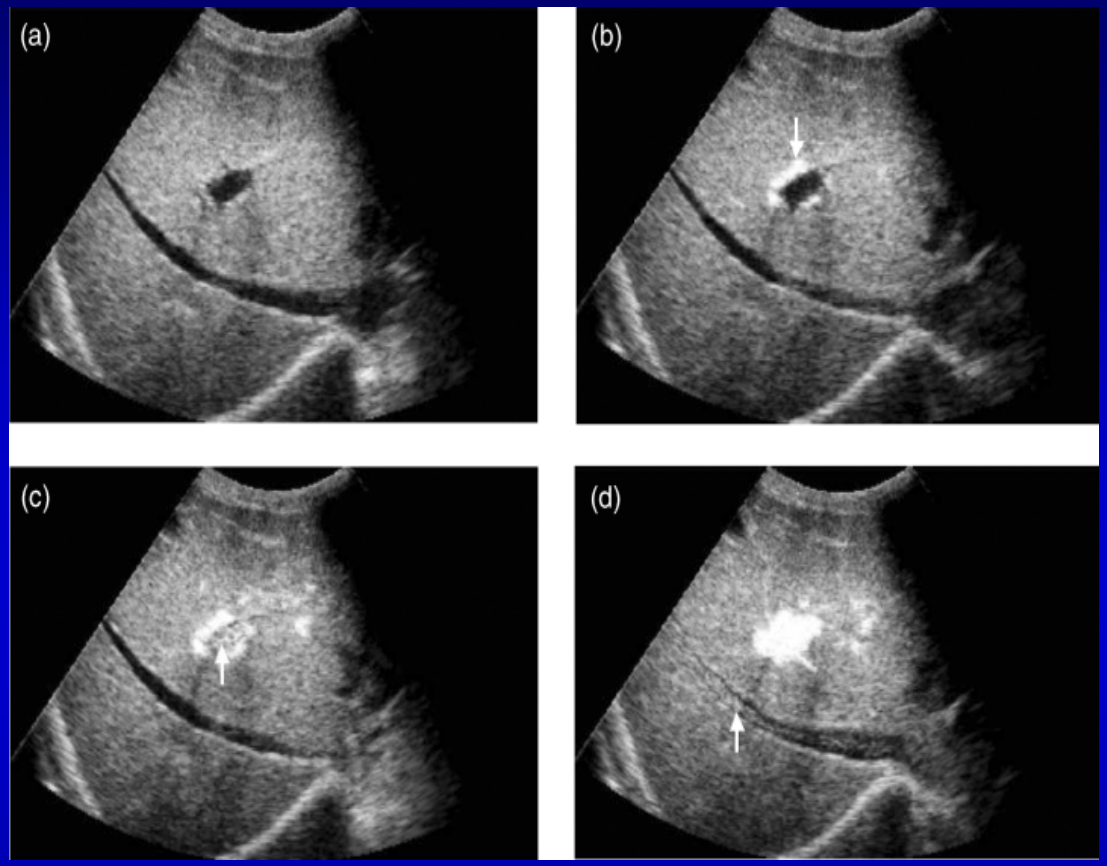
PATTERN TRIFASICO



PATTERN PIATTO

A typical example of pulse-inversion imaging

Hirota et al., Liver International, 2005



Just after a bolus injection of Levovist, a right-sided hepatic artery (HA), portal vein (PV), and right hepatic vein (RHV) were simultaneously scanned in a transverse section (a). First, the HA (arrow) was markedly enhanced after 15 s (b), then the PV (arrow) after 18 s (c), and finally, the RHV (arrow) after 37 s (d).

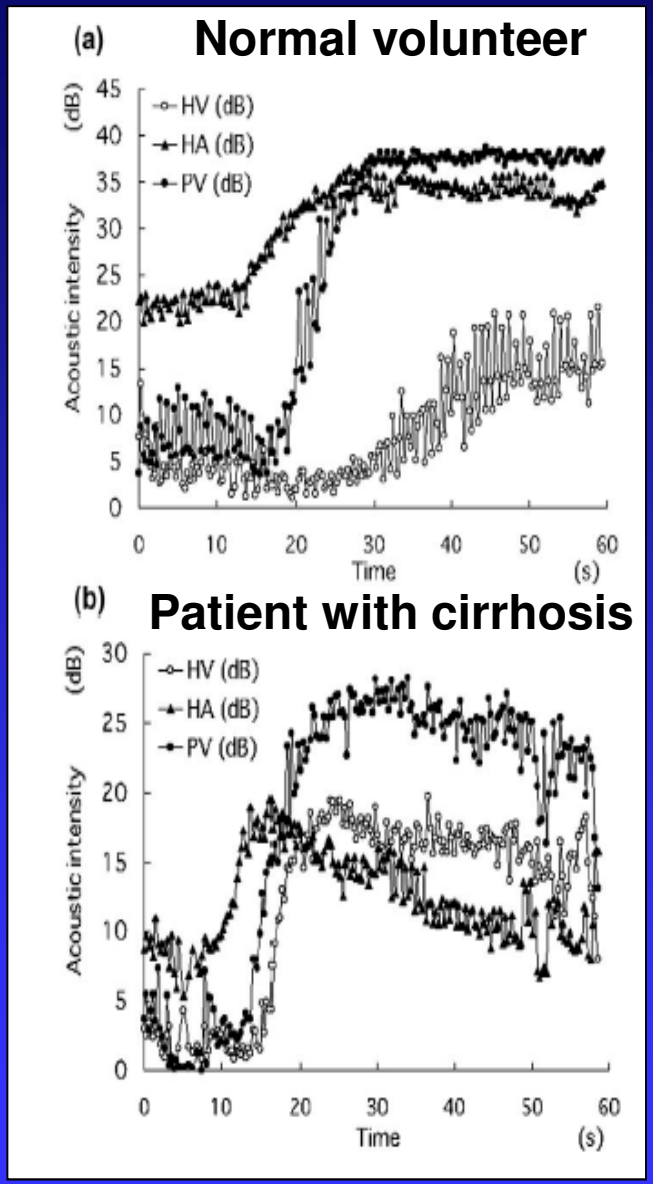
There is no differences in HA and PV time-acoustic intensity curves between a cirrhotic patient (b) and a normal volunteer (a).

On the other hand, the HV time-acoustic intensity curves between a cirrhotic patient and a normal volunteer is clearly distinguishable.

The HV time-acoustic curve in a cirrhotic patient demonstrated an earlier arrival time than that in a normal volunteer.

This difference is almost entirely caused by intrahepatic hemodynamic changes.

Sugimoto et al. J Hepatol 2002



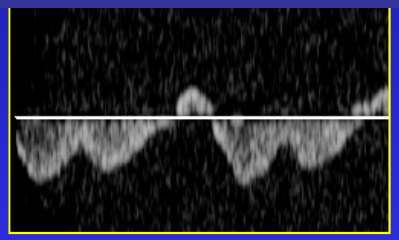
- RESULTS -

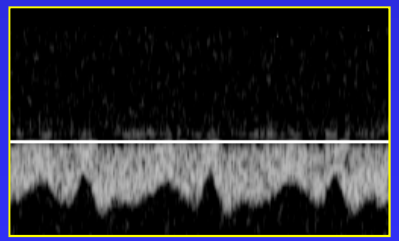
HVTT resulted earlier when MELD, Child-Pugh score and spleen diameter increased.

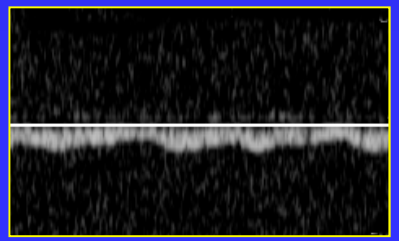
It was found a significant difference of transit times between patients with splenomegaly (mean diameter: 162.72 mm; HA-HVTT mean: 6.11 s; PV-HVTT mean: 1.54s) and cirrhotics with normal spleen diameter (mean diameter: 95.60 mm; HA-HVTT mean: 10.39 s; PV-HVTT mean: 6.73 s) ($p<0.01$ for HA-HVTT and PV-HVTT).

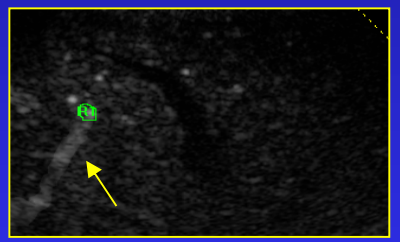
It was found e trend to the significant difference between the transit time and the degree of oesophageal varices in cirrhotic patients.

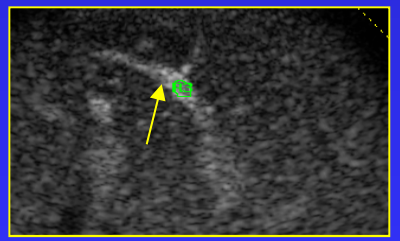
METHODS:We enrolled 26 participants who gave their informed consent: 22 cirrhotics and 4 healthy controls. Doppler shifts signals were obtained from right hepatic vein, using an intercostal scan during end - expiration breath holding**. *To characterize hepatic vein pattern we used an hepatic vein waveform index (HVWI), raising with increasing pulsatility of the waveform. This index is calculated as max vel – min vel / max vel and becomes >1 with the appareance of the triphasic waveform* (*Fig. 1*)**. We recorded out a clip from 20s before to 2min after a peripheral intravenous bolus injection of 2.4ml of SonoVue® (Bracco, Milan). Transit time analysis was perfomed and analysed by a quantification software package. ***We traced the region of interest (ROI) on a branch of hepatic artery, portal and hepatic vein, simultaneously scanned in an intercostal section (Fig 2). The arrival time in the three vessels was defined as the interval from the time of injection and the point of the curve with a signal intensity that exceeds baseline intensity by 10 % and followed by a clear further rise (Fig. 3).*** The time employed by USCA to cross liver from hepatic artery and portal vein to hepatic vein was defined as HA-HVTT and PV-HVTT.

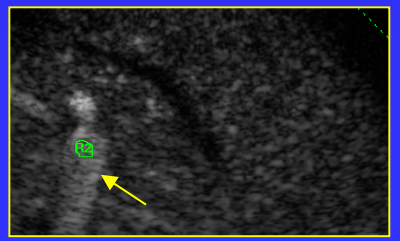


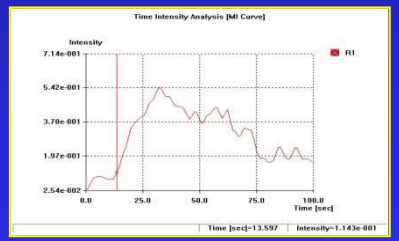


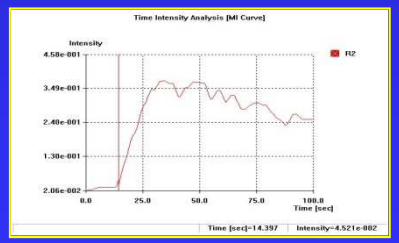


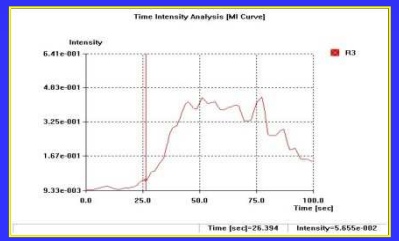












Conclusions

✓ Abnormal hepatic vein Doppler waveform in cirrhotic patients could be due to intrahepatic shunts rather than to lack of liver compliance.

✓HVTT could be useful in the non invasive evaluation of portal hypertension.

(Siciliani L, Rapaccini GL, J Ultrasound, march 2017)

Alternative non invasive alla biopsia epatica nelle CLD

- *Tests sierici di fibrosi*
- *Perfusion methods*
- *Fibroscan, Transient elastography*

⇓

"… the use of liver biopsy is recommended until clearly superior methodologies are developed and validated "

(AASLD Guidelines, Hepatology 2009)

Metabolic syndrome and HCC

- ✓ The progression of fatty liver to cancer is possible even without steatohepatitis or cirrhosis
- ✓ Obese and diabetics have higher risk of liver cancer
- ✓ Genetic factors may explain differences in regard onset and progression of liver disease
- ✓ New biomarkers may be useful in NAFLD

Liver fat and MRI

- *Di Martino M et al, World J Gastr 2016 : «Magnetic Resonanance Spectroscopy analysis correlates with histology in fatty liver»*

- *Bhat V et al, J Clin Diagn Res 2017 : «Subjects underwent sonography, CT, MRI and liver biopsy → MRI correlates with fat histological grading and is more accurate than CT.»*

- *Kὺhn JP et al, Radiology 2017 : « Measurement of liver fat and liver iron content by proton density fat fraction in 2561 subjects»*

↓

«In a white selected German population the prevalence of fatty liver disease and liver iron overload is 42,2% and 17,4% respectively»

Imaging ed epatopatie croniche

- *L' imaging non formula la diagnosi di epatopatia diffusa*
- *L'imaging conferma la diagnosi di epatopatia diffusa ed esclude altre patologie*
- *L'imaging contribuisce alla valutazione di gravità dell'epatopatia diffusa (RM : quantizzazione del danno ??)*
- ***L'imaging formula la diagnosi di complicanza dell'epatopatia diffusa : ipertensione portale, ascite, "impending" HRS, HCC (?!?!)***

S. metabolica, malattia cronica di fegato e sorveglianza per HCC

- Gli attuali programmi di sorvegliaza per la diagnosi «precoce» di HCC non sono mutuabili nella malattia cronica di fegato metabolica.
- L'ecografia non è uno strumento idoneo a studiare tali pazienti.
- La RM potrebbe avere una elevata accuratezza diagnostica… ma nessun DEF la contemplerebbe! Però….

….nuove tecnologie a ultrasuoni si stanno sviluppando in previsione della «epidemia» di sovrappeso prossima ventura

↓

- *Deep Abdominal Transducers : DAX technology (1-1,5 MHz)*
- *Improvement of 30% in penetration (40 cm.!)*

↓

Algoritmi di diagnosi e sorveglianza per tale popolazione di pazienti tutti da costruire !

EPATOPATIE DIFFUSE

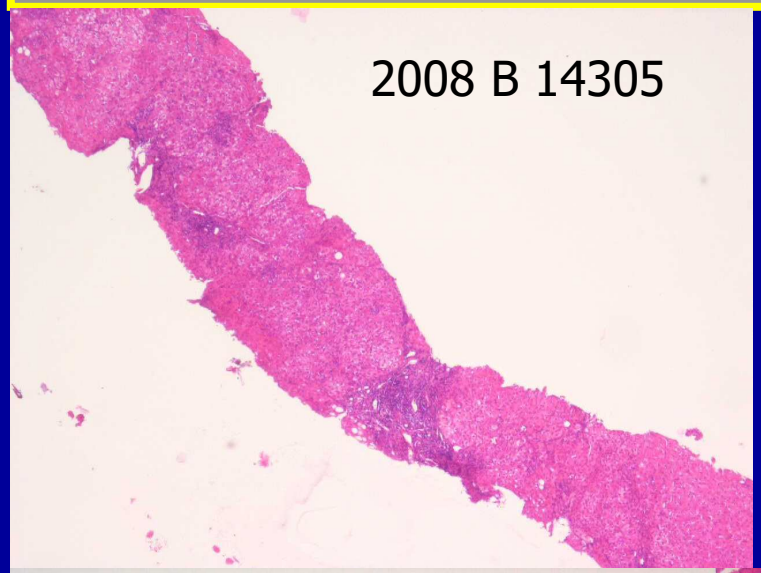
- Rappresentano uno dei più frequenti motivi di richiesta di ecografia addominale
- Principali cause: ***virus*** (HAV, HBV,HCV*,HEV) m.autoimmunitarie, ***m. metaboliche***, ***alcol***, tossici, farmaci, ischemia-ipossia, malattia veno-occlusiva, s. di Budd-Chiari
- * HBV : DNA HCV : RNA

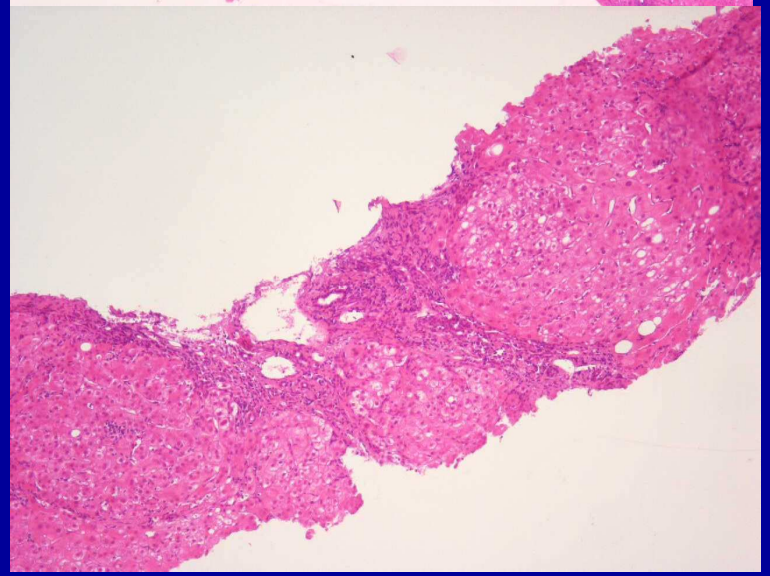
HCC : aetiopathogenesis

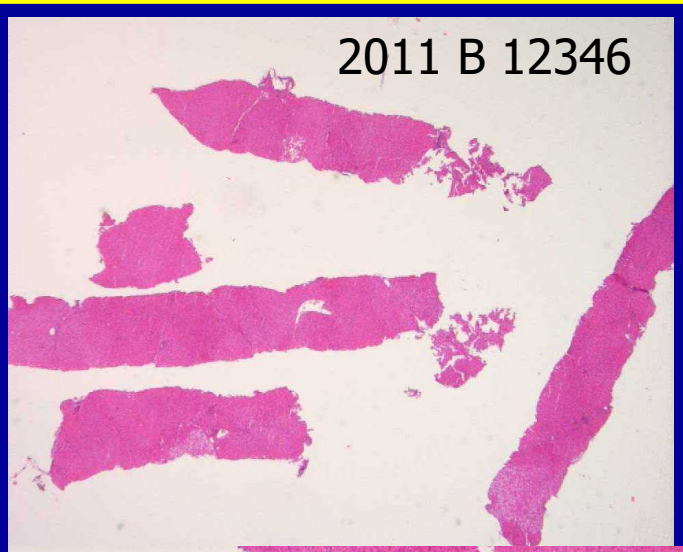
- HBV (HBsAg, HBcAb) : HBV-DNA (!) → direct mutagenic agent !!
- HCV (HCV-RNA!) : 53-76% in HCC through ***cirrhosis***.
- Alcohol : dose-dependent hepatotoxic effect!
- Aflatoxin B1 (mold of cereals) → mutation of codone 249 of oncosuppressor gene p53
- Emocromatosis (iron storage into the liver)

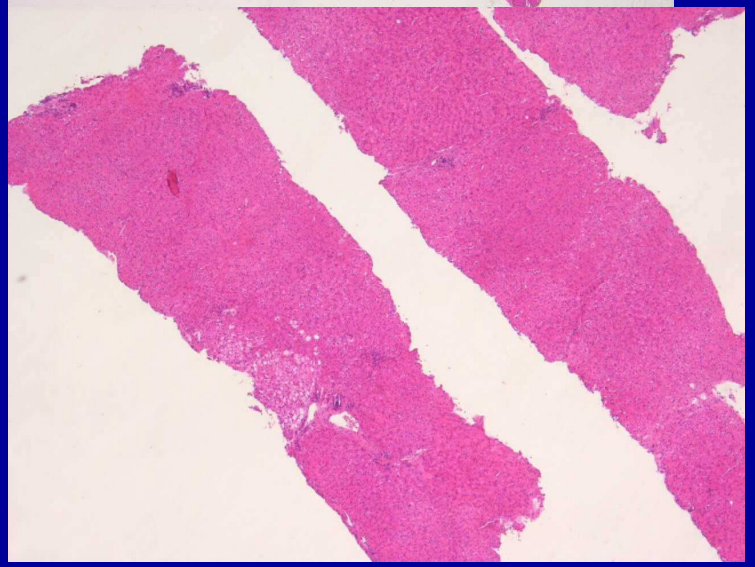
- PBC (Primary Biliary Cholangiopathy), autoimmune hepatitis, Metabolic syndrome !!
- Estrogens, anabolic drugs

Reversibilità della Fibrosi









«The influence of HIV infection in the natural history of HCC : results from a global multi-cohort study» Pinato DJ et al., JCO, in press

- 1588 advanced HCC from Europe, North and South America and Asia : 132 with HCV-HBV/ coinfection

- Prognostic factors for OS (4 months) in HIV+ : CTP class, α-FP, BCLC stage , HIV viral load, CD4+ concentration

↓

« HIV infection adversely influence the clinical course of HCC, leading to 24% in the hazard of death in patients who did not receive any active anticancer treatment»

↓

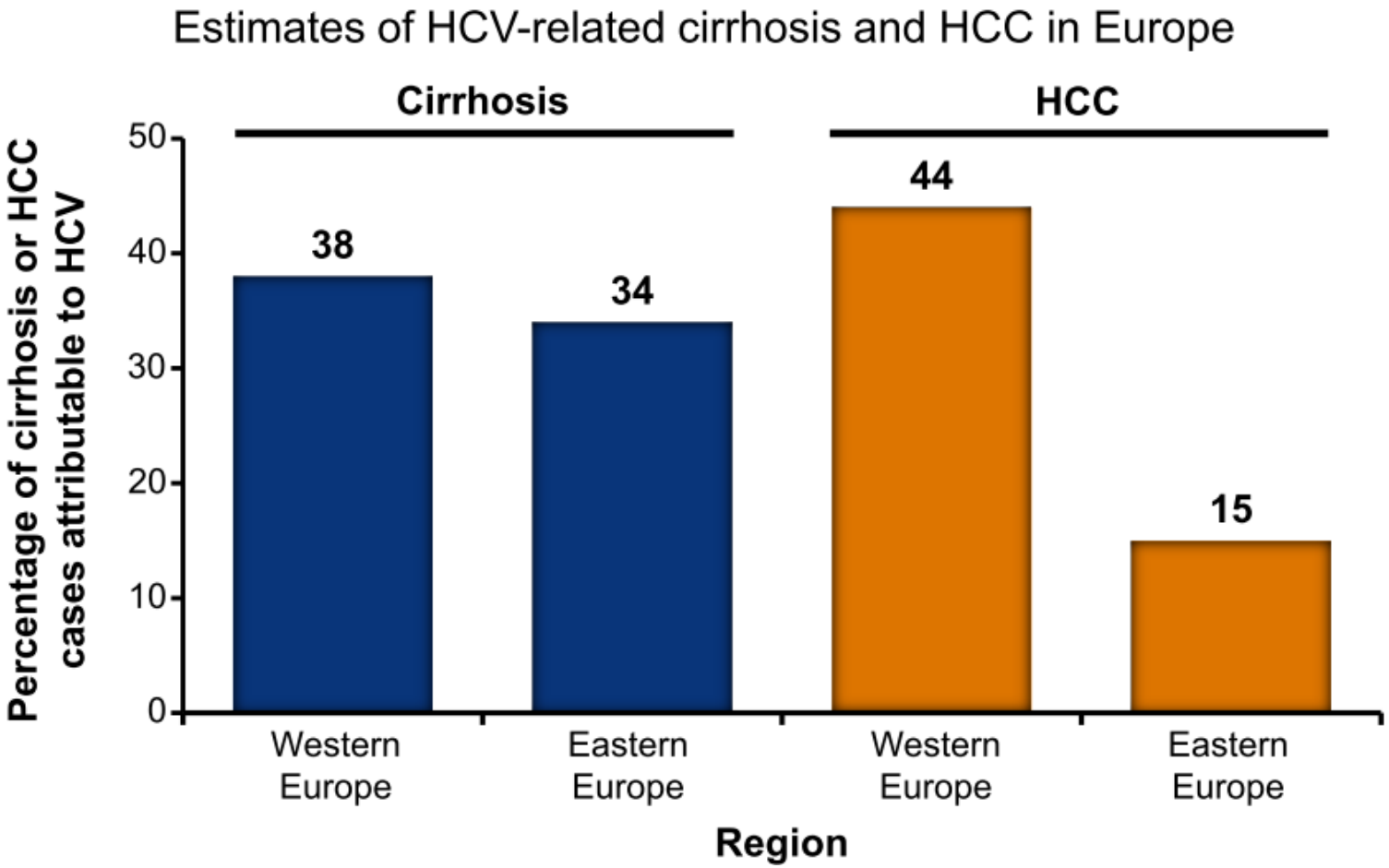
« HIV coinfected patients are a special population in terms of surveillance, diagnosis, prognosis and treatment of HCC»

HCV screening rates: 2011 estimation

	Belgium	France	Germany	Italy	Spain	UK
HCV screening, %						
Observed, % (year)	37 (2000)	57 (2004)	40 (2004)	40 (2005)	33 (2008–9)	30 (2004)
Estimated in 2011, %	50	64	48	46	35	34
HCV Genotype						
G1, %	60	56	60	62	65	44
G2/3, %	27	32	37	34	23	53
Other genotypes, %	13	12	3	4	12	3

Deuffic-Burban S, et al. Gastroenterology 2012 Oct;143(4):974-85.e14

HCV infection is associated with a significant health burden



Perz JF et al. J Hepatol 2006;45:529–38

Chronic HCV infection : liver disease.. extrahepatic disease.. systemic disease !

- *3% of the world's population are chronically infected*
- *The estimated liver-related mortality because of cirrhosis and liver cancer is 350.000 people/year*
- *Approximatly 74% of patients have extrahepatic manifestations of various degree (Cacoub P et al.,Arthr Rheumat,1999)*

↓

↗ *hepatotropism*

HCV

↘ *lymphotropism*

(Dammacco F et al., Semin Liver Dis, 2000)

Infezione da HCV

Possibile successione degli eventi

↓

Infezione

↓

Stimolazione sistema immune

↓

Crioglobulinemia mista (tipo II, tipo III)

↙ ↘

disordini autoimmuni *linfoma (B-NHL)*

(associazione HCV/B-NHL = 2,4-42%)

PATOLOGIE ASSOCIATE A CRIOGLOBULINEMIA

Type I
Multiple myeloma
Waldenström's macroglobulinemia
Other lymphoproliferative diseases with M components
Type II
Chronic hepatitis C virus infection
Sjögren's syndrome
Waldenström's macroglobulinemia
Chronic lymphocytic leukemia
Non-Hodgkins' lymphoma
Autoimmune diseases
Cold agglutinin disease
Type III
Chronic infections
Viral (EBV, CMV, HIV, **hepatitis viruses**)
Bacterial (subacute bacterial endocarditis, leprosy, spirochetal)
Fungal, parasitic
Autoimmune diseases
Systemic lupus erythematosus
Rheumatoid arthritis
Inflammatory bowel diseases
Biliary cirrhosis

Kallemuchikkal & Gorevic, Arch Pathol Lab Med 1999, 123:119-25

Crioglobuline e HCV

- Le crioglobulinemie HCV-relate, sono correlate a manifestazioni cliniche proprie che Meltzer e Franklin individuarono nella triade **porpora, artralgia e astenia,** ma che coinvolgono in varia misura altri organi ed apparati.
- Sono presenti in correlazione a HCV-Ab (maggiore prevalenza nel Tipo II).
- Il virus è patogeneticamente coinvolto, essendo stato ritrovato come RNA nel crioprecipitato.

Crioglobulinemia : diagnosi

" Riscontro di precipitati proteici nel siero mantenuto a 4° C per almeno 7 giorni, che scompaiono ritornando alla temperatura di 37° C. I crioprecipitati sono costituiti da IgG policlonali con IgM monoclonali o policlonali con attività del fattore reumatoide (tipo II o tipo III rispettivamente)"

«…caposala, ma quando arrivano queste crio? Sarà una settimana che abbiamo mandato il campione!»

« Useful biomarkers for assessment of hepatitis C virus infection-associated autoimmune disorders»

(Yang Dh et al., WJG, 2014, 21; (20)11: 2962-70)

Autoanticorpi rilevabili nell' infezione cronica da HCV:

- ✓ *Fattore reumatoide*
- ✓ *Anticorpi antinucleo*
- ✓ *Anticorpi anti – SSA/-SSB*
- ✓ *Anticorpi anti-citoplasma dei neutrofili*
- ✓ *Anticorpi anti-muscolo liscio*
- ✓ *Anticorpi anti-LKM1, anti-tireoglobulina, anti-TPO….*

↓

..iperattivazione e proliferazione dei linfociti B, mediante l'interazione con le proteine di superficie di HCV

Patologia d'organo correlata alla crioglobulinemia in corso di infezione cronica da HCV

- *Cute → porpora, ulcere arti inferiori…*
- *Sistema nervoso → neuropatia periferica, SNC*
- *Polmone → fibrosi interstiziale*
- *Rene→glomerulonefrite (membranoproliferativa)*
- *Cuore → pericardite, coronarite, valvulopatie*
- *App.digerente→vasculite mesenterica (epatite)*
- *App. locomotore → poliartrite*
- *Ghiandole salivari, lacrimali → Sicca Syndrome*
- *Diabete, insulino-resistenza*
- *Tiroide → tiroidite autoimmune*

Autoanticorpi e manifestazioni cliniche nell'infezione cronica da HCV

- ✓ *Porpora, ulcere →crioglobuline, ANCA (LES)*
- ✓ *Glomerulonefrite →ANCA, anti-dsDNA (LES)*
- ✓ *Poliartriti → RF, anti-CCP (AR)*
- ✓ *SS → anti-SSA/SSB*
- ✓ *Epatite → anti-SM, anti-LKM1 (Epatite autoimmune)*

La terapia dei disordini immunologici presenti nell'infezione cronica da HCV è la cura dell'infezione da HCV ?

- *Molti dei sintomi e dei disordini immunitari presenti nell'infezione da HCV migliorano (guariscono?!?) con l'eradicazione del virus (Gragnani L et al., Dig Liv Dis, 2014)*
- *In una percentuale variabile di pazienti (?) le manifestazioni extraepatiche permangono irreversibili con persistenza della crioglobulinemia mista*
- *Tale osservazione sembra permanere anche dopo l'introduzione dei nuovi antivirali (Boceprevir, Telaprevir,* ***Sofosbuvir*** *)*
- *La maggior parte di tali pazienti hanno la cirrosi (maggior durata del trattamento in tali pazienti?)*

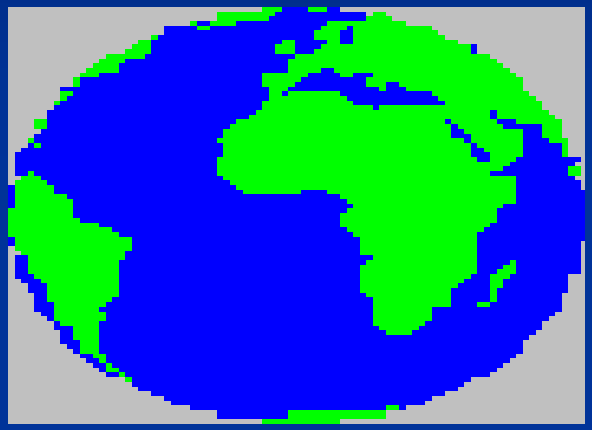
Infezione da HCV, fegato e manifestazioni extraepatiche

↓

”…gentile paziente, nel panorama delle patologie dovute alla sua infezione da virus C dell’epatite, forse l’epatite non è il maggiore dei problemi !”

EPIDEMIOLOGIA

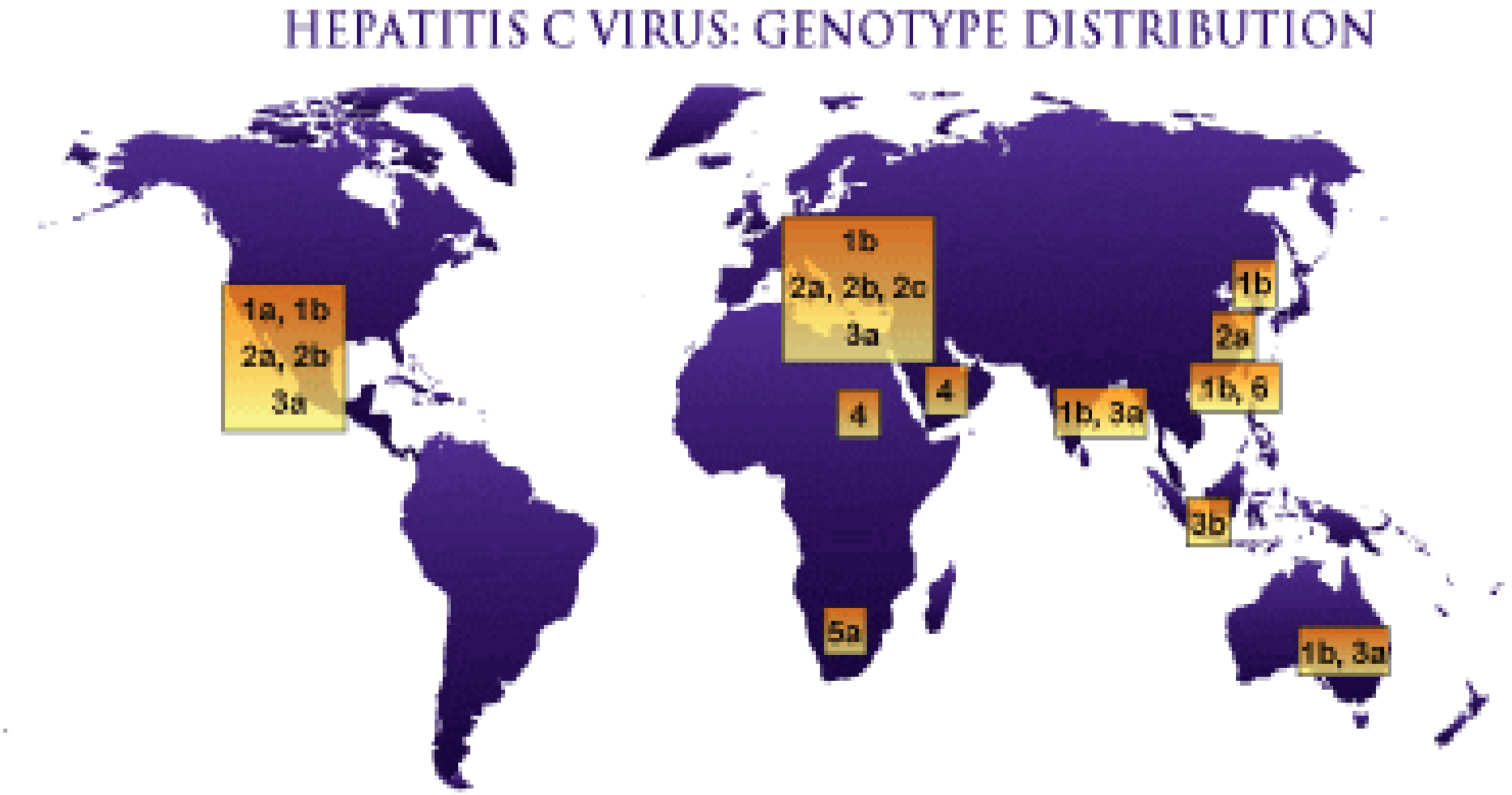
La diffusione dell'HCV è elevata in tutto il mondo .



3% della popolazione mondiale,
160-200 milioni

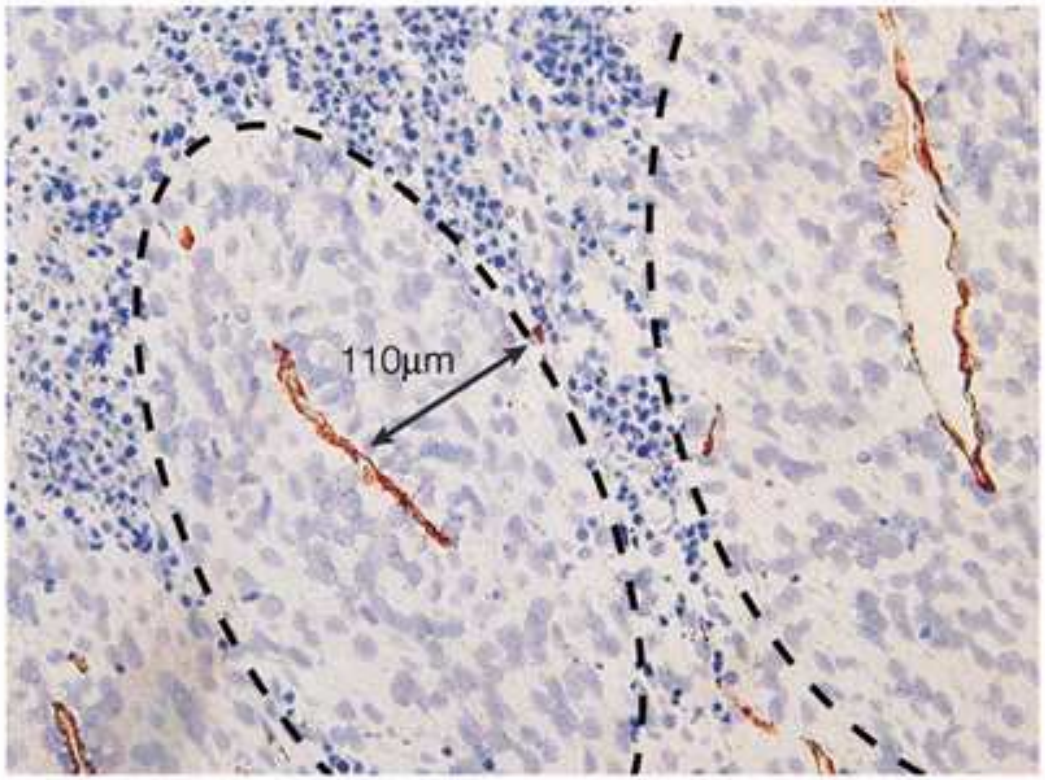
- 3-12 % della popolazione con gradiente che cresce in senso nord-sud e con l'età

La distribuzione geografica dei diversi genotipi dell'HCV



Fang *J. Clin Liver Dis.* 1997.

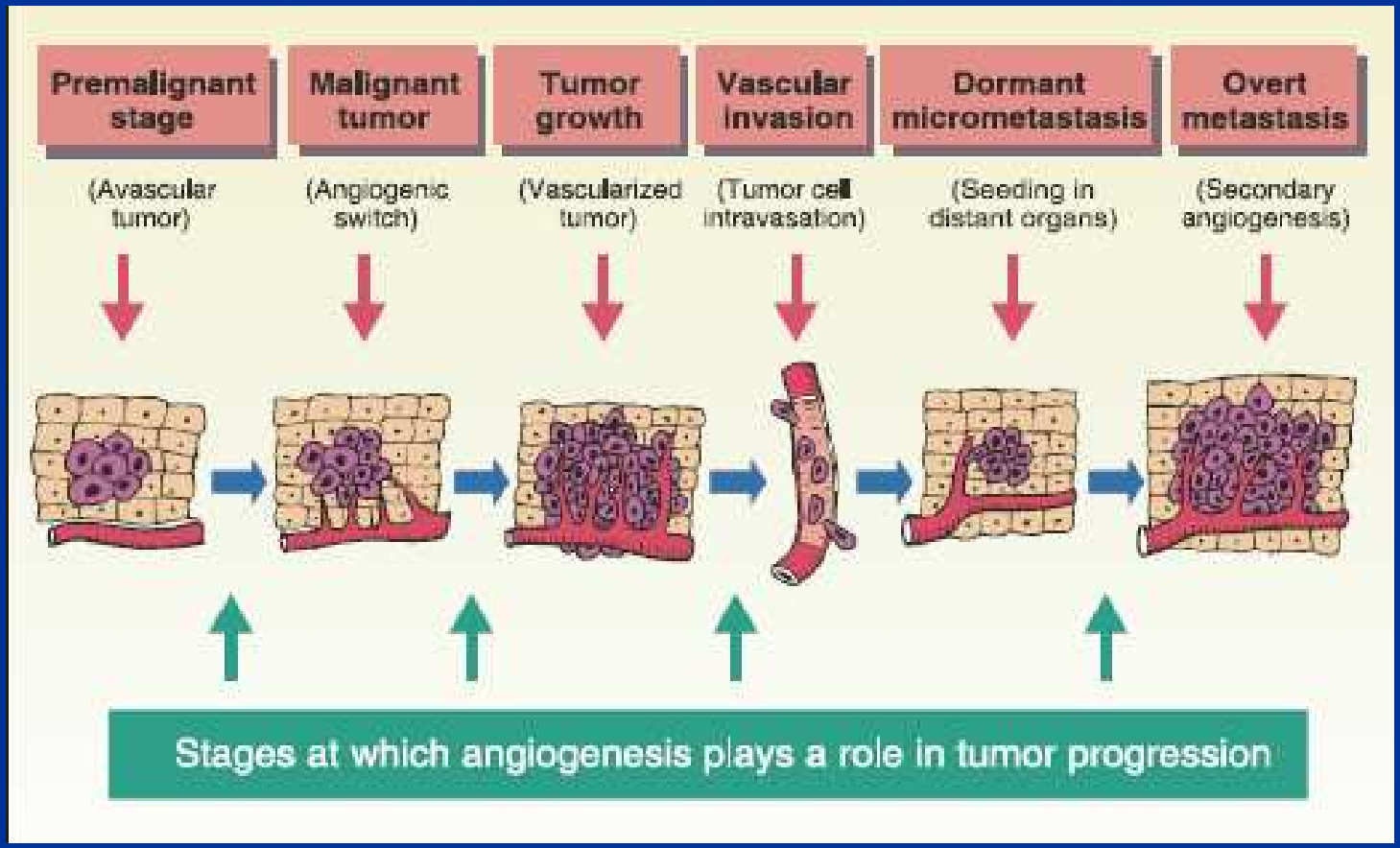
Neoangiogenesis is essential to tumour growth



Folkman, *Nature Rev Cancer* 2002

Anti-angiogenic drugs in HCC

Angiogenesis is a complex, multistep process initiated by the release of angiogenic factors (VEGF, PDGF, FGFbeta, etc) from tumour cells and surrounding stromal cells



Pang, Cancer letter 2006

OBI Clinical Impact

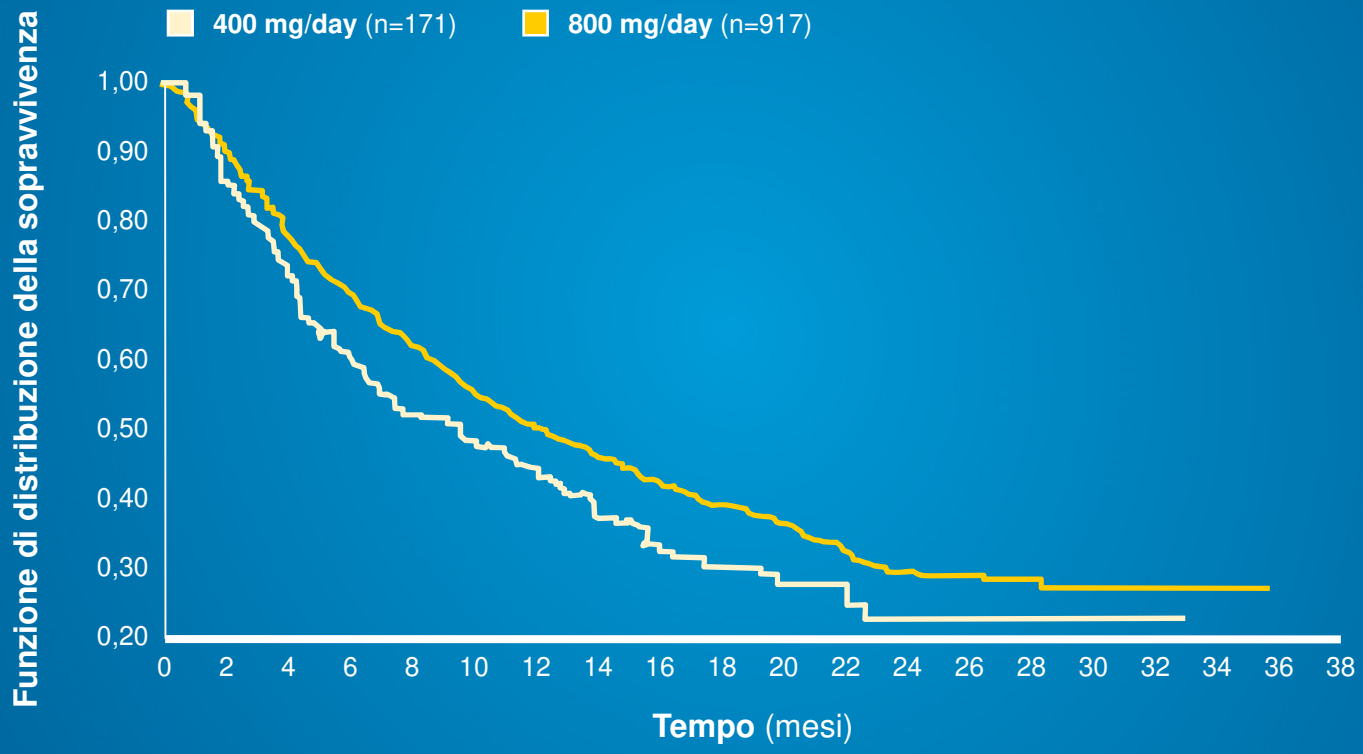
Occult HBV infection may…

Consequence: typical hepatitis B in the recipient

Consequence: typical hepatitis B in the OBI carrier

Sorafenib: dosaggio e sopravvivenza nella pratica clinica

Overall survival according to initial sorafenib dose
European subset

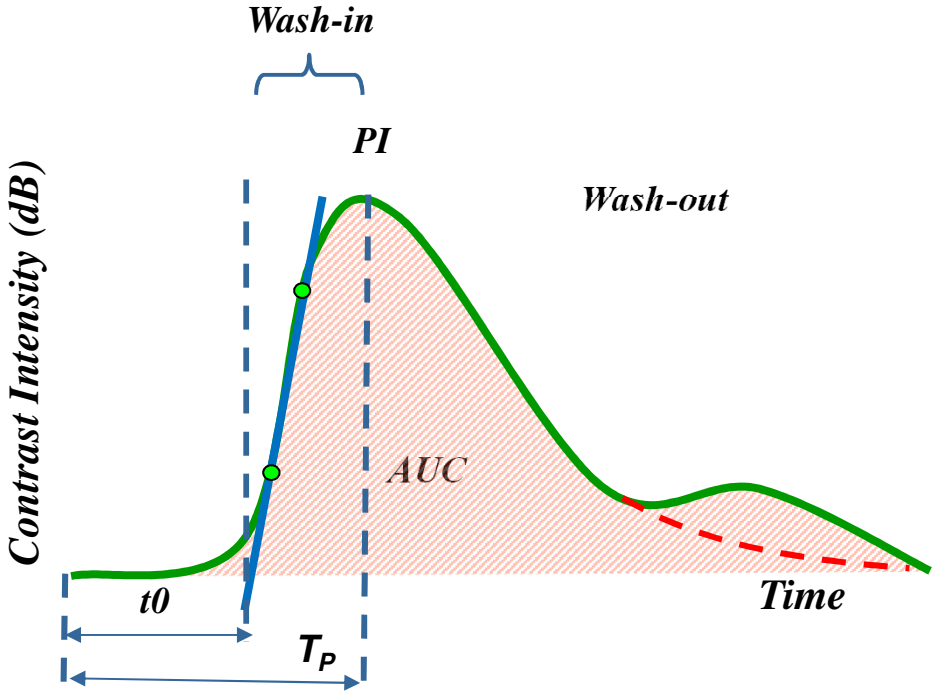


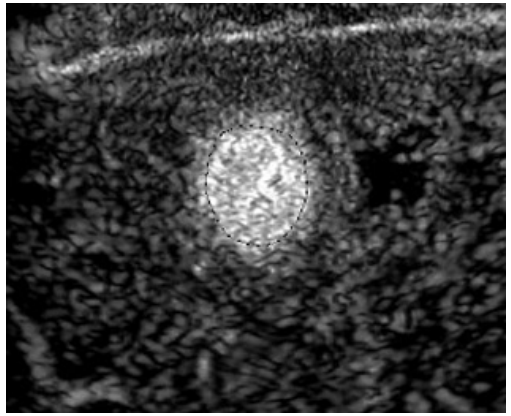
400 mg pts: more C-P B and ECOG 1!!

Daniele B, et al. Eur J Cancer 2013; 49(Suppl 2): abs. 2581.

Contrast Enhanced UltraSound

- Analysis and placement of ROIs -



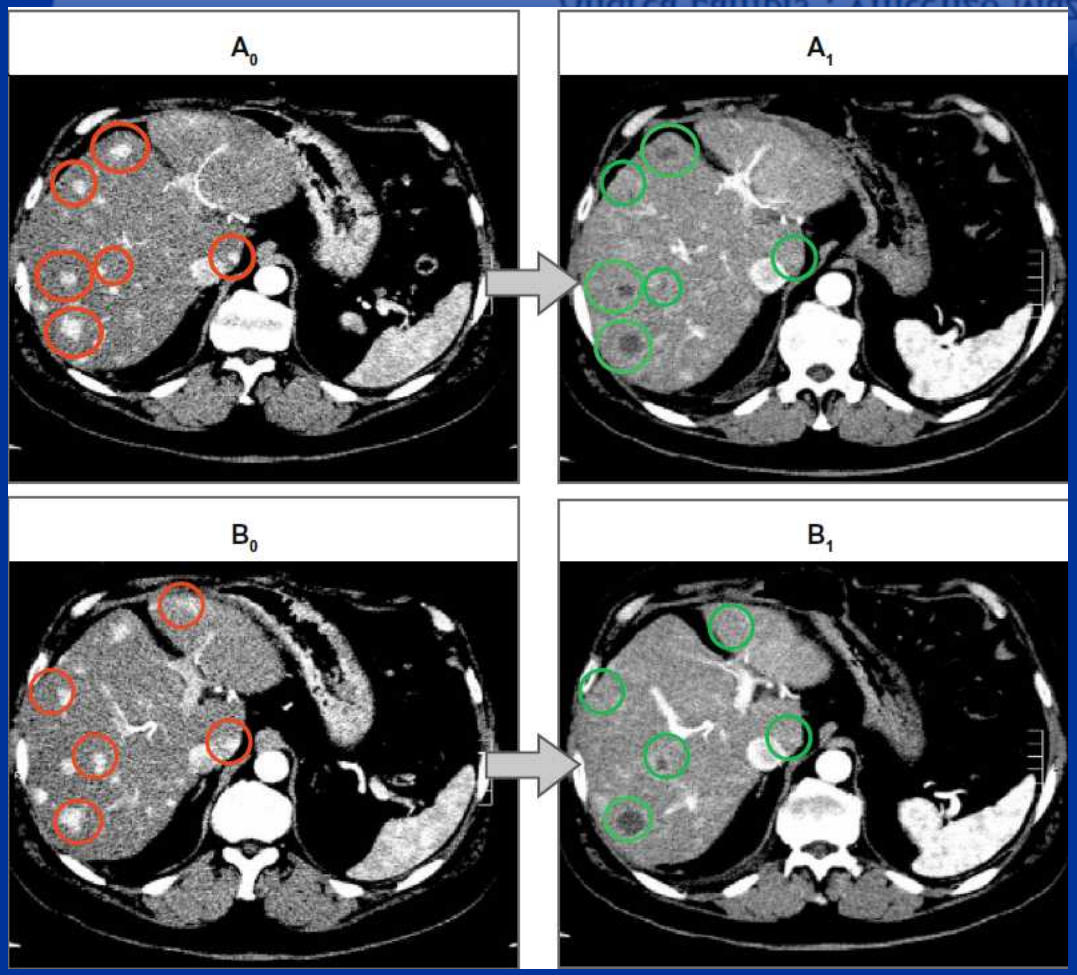


- ✓ ***PI*** (peak intensity) in AU
- ✓ T_P (time to peak intensity) in sec
- ✓ ***AUC*** (area under the curve) in AU
- ✓ T_P (slope coefficient of wash-in) ***in*** AU/sec
- ✓ ***MTT*** (mean transit time) in sec

Perfusion parameters extracted from time-intensity curves

Personalized molecular targeted therapy in advanced, recurrent hepatocellular carcinoma after liver transplantation: A proof of principle

Sherrie Bhoori[1], Sara Toffanin[1,2], Carlo Sposito[1], Alessandro Germini[1], Alessandro Pellegrinelli[1], Andrea Lampis[1], Vincenzo Mazzaferro[1,*]



Treatment with Sorafenib+mTOR inhibitors was started.

3 months later CT scan showed a 50% response according to mRECIST criteria

Future Burden ?!?

- *Epidemiologia futura*
- *Impatto dei trattamenti con DAA sulla malattia cronica di fegato e sue complicanze*
- *Management dopo SVR*
- *Obiettivi futuri*

Epidemiologia dell'Epatite HCV

- *2-3% della popolazione mondiale (120-180.000.000)*
- *Prevalenza : < 1.5% (Nord America) – 22% (Egitto)*
- *Risoluzione spontanea : 20-30%*
- *Infezione cronica : 70-80% (IL28B !)*
- *Trasmissione : prevalentemente sangue infetto*
- *Rischio dopo l'introduzione della PCR per HCV-RNA : 1:500.000 – 2.000.000 trasfusioni (?!?)*

↓

WHO : inclusion of new HCV drugs in the list of essential medicines→ sustainable development goal (SDG) until 2030 (Waheed Y, Pathog Glob Health, 2015)

HCV epidemiology in 2011: estimation of number of patients ever infected

Deuffic-Burban S, et al. Gastroenterology 2012 Oct;143(4):974-85.e14

«Future burden of the Disease »

- *Futura nuova epidemiologia*
- *Impatto dei trattamenti con DAA sulla cirrosi, sulle sue complicanze (HCC, insufficienza epatica…) e sulla sopravvivenza*
- *Reversibilità della fibrosi (??)*
- *Management dopo SVR*
- *Rischio di reinfezione*
- *Eradicazione worldwide (2030-2040 ?!) : programmi di screening (?!)*
- *Costo dei trattamenti….*

Trattamento della malattia cronica di fegato e incidenza di HCC

- *I trattamenti antivirali (IFN ± RIBA), con SVR, hanno ridotto (ma non azzerato!) l'incidenza di HCC*
- *Rimangono fattori di rischio la fibrosi grave (cirrosi), l'età avanzata, il diabete, l'obesità*
- *I trattamenti IFN-free ottengono una SVR > 90%, ma la loro efficacia nel ridurre l'incidenza di HCC va dimostrata (in ricerca in Medicina non esiste la proprietà transitiva…)*
- *I pazienti con cirrosi che anche abbiano ottenuto una SVR devono proseguire il programma di sorveglianza per HCC!*

"Hepatitis C eradication : a long way to go"
(Waheed Y, World J Gastroenterol, 2015)

- *The actual production cost of a 12 wk regimen of DAA is about $ 250*
- *1 premature death is prevented for every 3 virologic cures*
- *47% of blood donations in low income countries are from laboratories with no quality assurance (III generation EIA) (WHO)*
- *40% of global HCV infections are due to unsafe injections and medical equipments.*

Valutazione della steatosi/fibrosi epatica

- *Marcatori sierologici*
- *Ecografia epatica*
- *Transient Elastography, Real-time Tissue Elastography.*
- *Angiosonografia (CEUS)*
- *CT, MRI, MR Spectroscopy*
- *ISTOLOGIA*

EPATOPATIE CRONICHE

STEATOSI EPATICA

- La degenerazione lipidica in alcuni casi colpisce solo alcune zone, simulando lesioni focali
- I quadri ecografici sono due:
  - Ipoecogeno: aree ovalari di varia dimensione; sedi tipiche anteriormente alla biforcazione portale e in sede paracolecistica (aree a diversa distribuzione lipidica) (Caturelli E. et al., Gastroenterology, 1992)
  - iperecogeno: aree voluminose occupanti interi segmenti (s. segmentaria) o parte di essi (s.subsegmentaria) oppure aree di minori dimensioni ma diffuse in entrambi i lobi (steatosi a prato fiorito)

Sviluppo di HCC: cfr trattati↔non trattati

Autore	*SVR*	*F-up*	*HCC*
Nishiguchi ,1995	*15,6%*	*53*	*T= 4%*
			U= 38%
Valla, 1999	*?*	*37*	*T= 11%*
			U= 18%
Bernardinello,'99	*5%*	*60*	*T= 5%*
			U= 4%
Azzaroli,2004	*43%*	*60*	*T= 0%*
			U= 30%
Soga, 2005	*32%*	*93*	*T= 5%*
			U= 23%

- *Metanalisi di trial e studi di coorte :l'incidenza a 5 anni trattati/non trattati si riduce del 7,8% (Shen,Oncology,2012)*

Terapia antivirale e rischio di recidiva dopo trattamenti «curativi» (resez/ablaz)

Autore	*n.casi*	*SVR*	*HCC*
Kubo, 2002	*30*	*13,3%*	*T = 34%*
			U = 80%
Shiratori, 2003	*74*	*29%*	*T = 68%*
			U = 77%
Mazzaferro,2006	*150*	*7%*	*T = 60%*
			U = 63%
Hsu,2013	*1.065*	*(a 5 aa.)*	*T = 52,1%*
			U = 63,9%

↓

La riduzione del rischio diventa statisticamente non significativa nei pz > 60 aa, con la cirrosi (?) o il diabete.

The impact of direct antiviral agents on the development and recurrence of HCC

Two topics:

1.Patients with cirrhosis who are at risk of developing HCC;

2.Patients at risk of developing recurrent HCC following successful resection, tranplantation or ablation

« HCC risk following DAAs HCV-therapy : a systematic review, meta-analyses and meta-regression» Waziry R et al., J Hepatol, 67 (6), 1204-1212, 2017

- *HCC occurrence and recurrence comparing DAA with IFN based therapy in SVR patients*
- *41 studies : - 26 HCC occurrence*
  - 17 HCC recurrence

- *HCC occurrence was 1.14/100 py and 2.96/100 py in IFN and DAA*
- *HCC recurrence was 9.21/100 py and 12.16/100 py in IFN and DAA*
- *In meta-regression adjusting for follow-up and age DAA therapy was not associated with higher HCC occurrence or recurrence*

↓

«..there is no evidence for differential HCC occurrence or recurrence risk following SVR from DAA and IFN-based therapy».

"REAL-TIME" TISSUE ELASTOGRAPHY

Recently, elastography has emerged as an option in several commercial ultrasound systems, and is starting to prove clinically valuable in many areas, particularly for example in assisting breast cancer diagnosis, or in guiding minimally invasive treatment of prostate cancer. The technique reveals the physical properties of the tissue by characterizing the difference in hardness between diseased and surrounding tissue.

The method measures mechanically induced deformation (strain) of structures in the B mode image to quantify the elasticity of the tissue. By measuring the tissue strain induced by compression, it is possible to estimate the tissue hardness.

« Sustained virologic response to DAAs therapy in patients with chronic hepatitis C and HCC : a systematic review and meta-analysis» (Ji F et al., J Hepatol, April 2019)

- *49 studies of 15 countries*
- *3.341 HCC and 35.701 non-HCC patients*
- *SVR was lower in HCC than in non-HCC (89,6% vs 93,3%)*
- *SVR was lower in active/residual HCC than in inactive/ablated HCC (73,1 % vs 92,6 %)*
- *HCC patients with prior OLT had higher SVR than non-OLT HCC patients*

↓

« SVR is lower in HCC compared to non-HCC patients»….but

↓

was high the heterogeneity of : - patients
- stage of HCC
- treatments of : HCC
DAAs

« DAAs after successful treatment of early HCC improve survival in HCV-cirrhotic patients» (Cabibbo G et ITA.LI.CA. , J Hepatol , June 2019)

- *204 HCV-related cirrhotic patients : 102 DAA treated , 102 DAA untreated.*
- *All patients had a diagnosis of HCC (BCLC stage 0/A) with complete radiologic response after resection or ablation.*
- *Mean follow-up of 21,4 months*
- *DAA group : 6,9% died*

27,5 % HCC recurrence

5,9% hepatic decompensation

↓

« DAAs significantly improved OS compared with no DAAs treatment, due to reduction of hepatic decompensation»

« Residual hepatitis C virus in peripheral blood mononuclear cell as a risk factor for HCC after achieving a SVR : a dogma or fiction» (Hanafy AS et al. Eur J Gastroenterol Hepatol, April 2019)

- **OCI** (Occult hepatitis C virus Infection): negative HCV antibodies and HCV-RNA in serum but positive for Hepatitis C core antigen (HCVcAg) and /or for HCV-RNA in liver biopsy or PBMCs .
- 89/824 (10,8 %) SVR24 patients developed hepatic decompensation in a follow-up period of 8,2±1,8 months
- HCV-RNA in PBMCs and HCVcAg were found in 95,5% and in 85,9% of the decompensated patients respectively
- 27,1% of patients with OCI developed recurrence of viremia (HCV-RNA in serum) after 3.57±1,34 months
- In the OCI group were significantly more frequent diabetes, thrombocytopenia and elevated pretreatment αFP.

↓

«..probably we have to reconsider the current definition of SVR»

Malattia cronica di fegato : istopatologia/metodi non invasivi

Elastosonografia

- *FIBROSI*

Istopatologia

- *Necrosi*
- *Infiammazione*
- *FIBROSI*
- *Colangiopatia*
- *Accumulo metalli*
- *Metaplasia/displasia*
- *Istochimica/immunoistochimica*
- *DNA virale intraepatocitario (HBV)*
- *(Attivazione cell. Kuppfer)*
- *(Dilatazione sinusoidi)*
- *…..*

Infezione da HCV

Possibile successione degli eventi

↓

Infezione

↓

Stimolazione sistema immune

↓

Crioglobulinemia mista (tipo II, tipo III)

↙ ↘

disordini autoimmuni *linfoma (B-NHL)*

(associazione HCV/B-NHL = 2,4-42%)