EVALUATION OF FIBROSIS AND STEATOSIS WITH NON INVASIVE METHODS

Comments from pathologist

Pierre Bedossa

Department of Pathology, Hôpital Beaujon,

University Paris-Denis Diderot

France

Inserm U 773

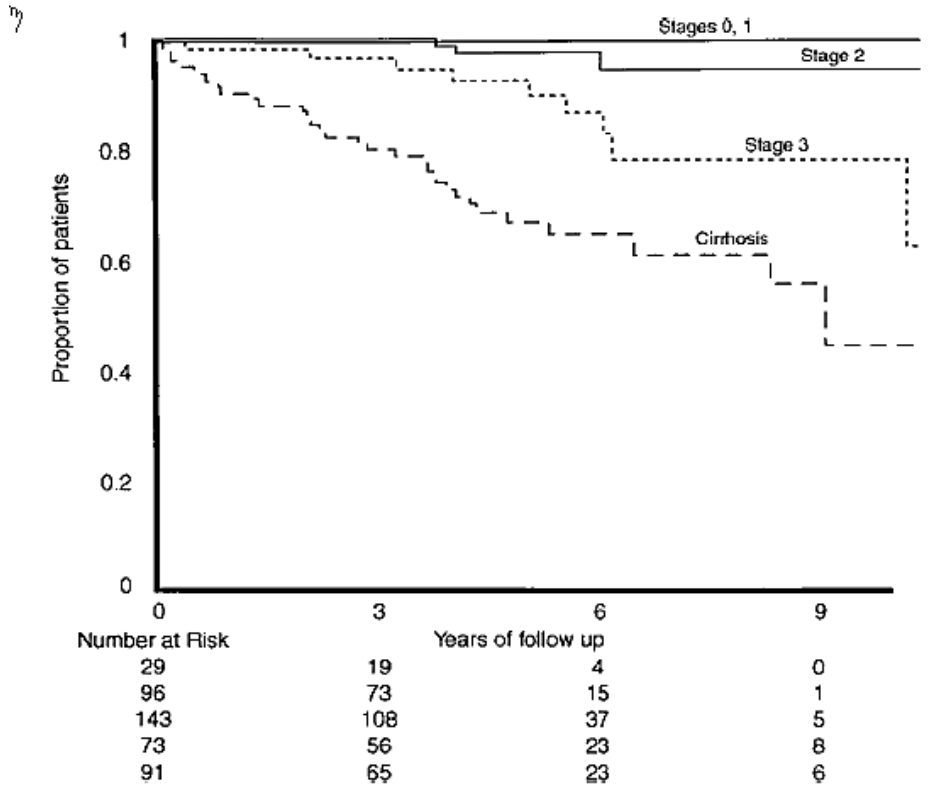
UNIVERSITE PARIS7- DENIS DIDEROT UMRS 773

EVALUATION OF FIBROSIS AND STEATOSIS WITH NON INVASIVE METHODS

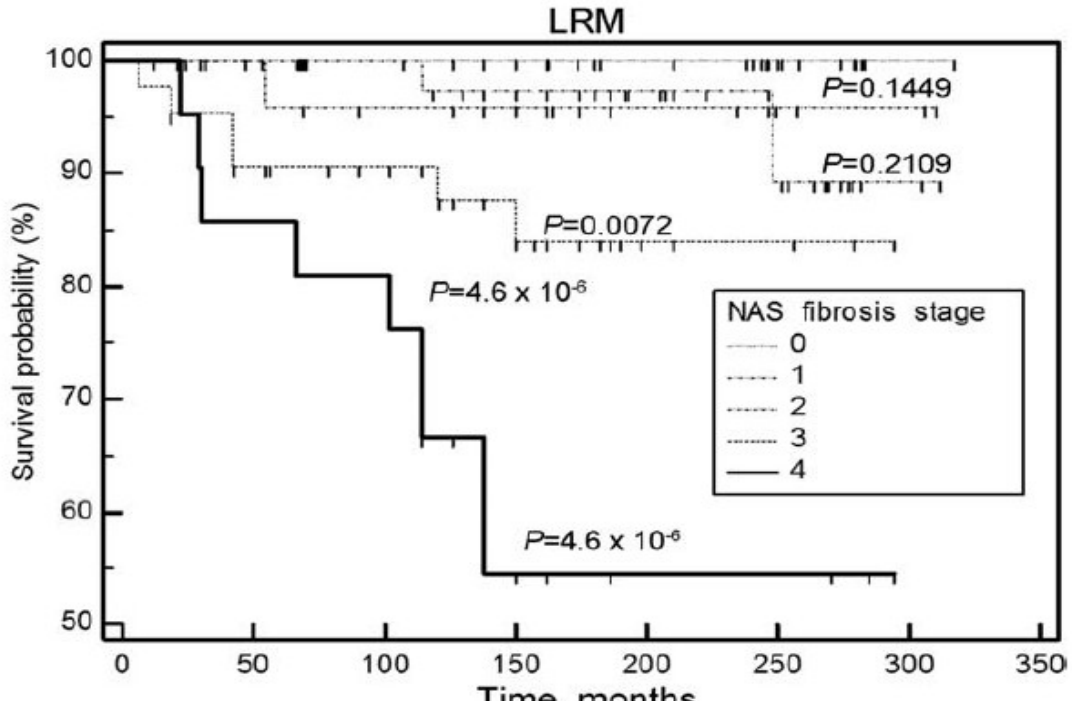
- To emphasize some important questions raised from pathology when discussing non invasive evaluation of :
  - FIBROSIS
  - STEATOSIS

Fibrosis : The major histological prognostic factor

Survival to liver-related complications according to liver fibrosis stage on initial biopsy in Hepatitis C

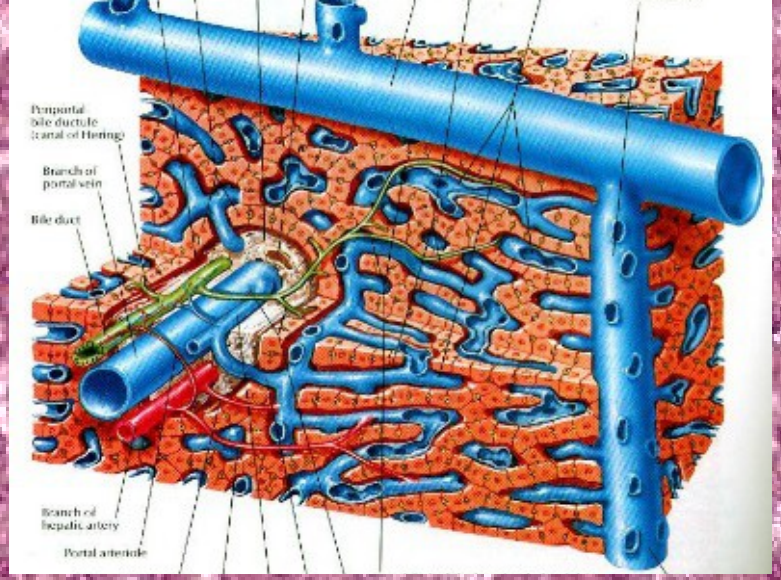


Histological stage of fibrosis predicts survival in NASH



MH. Khan et al. **Which patients with hepatitis C develop liver complications?** Hepatology 2000; 31:513-520

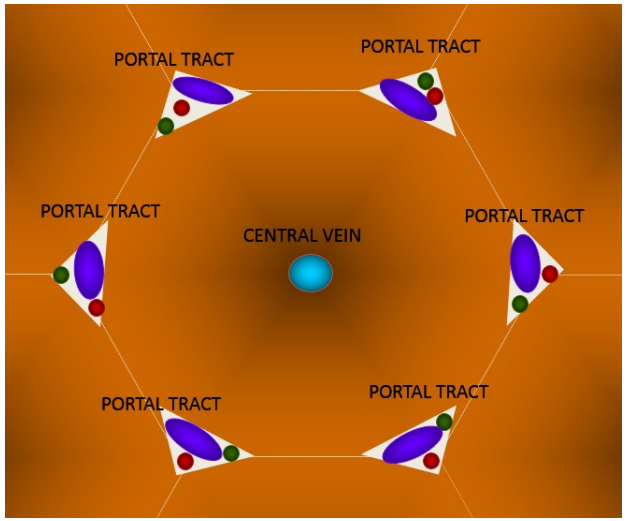
Younossi ZM, Stepanova M, Rafiq N, et al.. Hepatology 2011



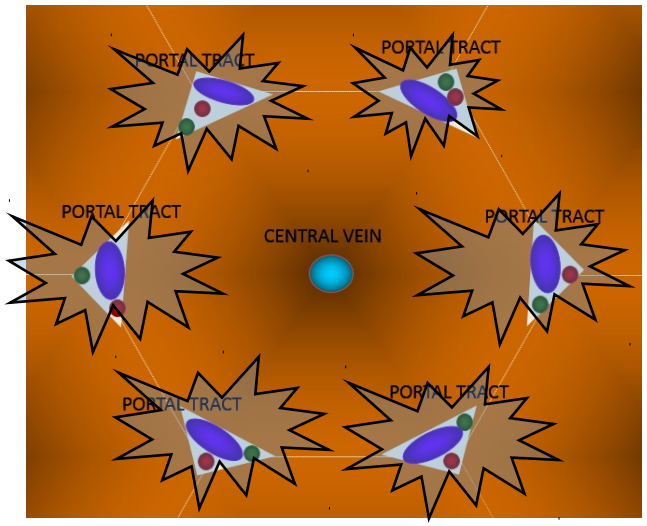
Normal liver, Masson’s trichrome

Comment 1 :NOT ALL FIBROSIS ARE ALIKE

NORMAL LIVER LOBULE

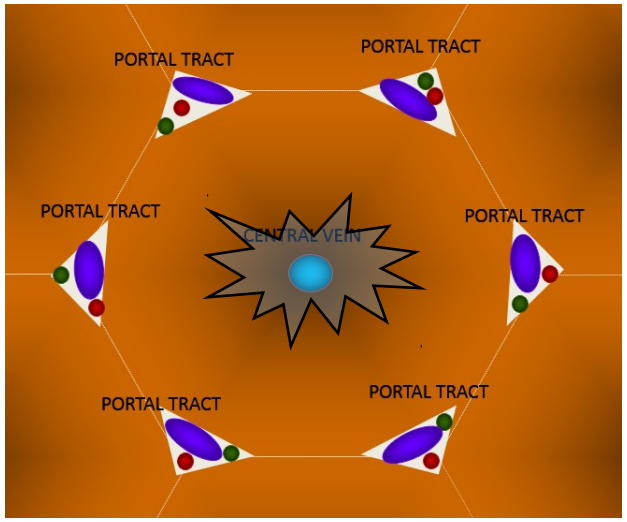


PERIPORTAL SPREADING FIBROSIS



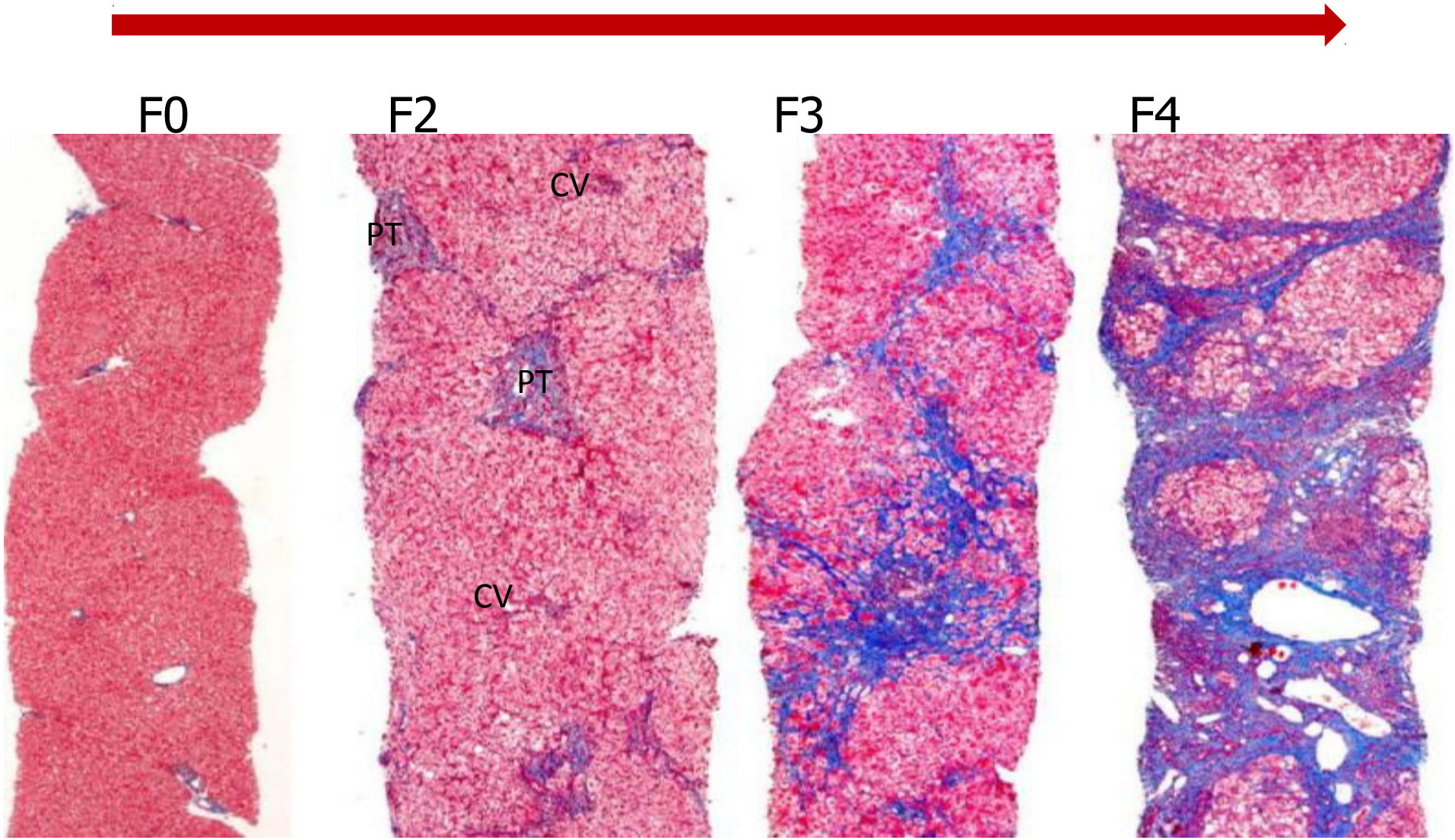
CHRONIC VIRAL HEPATITIS

PERICENTRAL SPREADING FIBROSIS

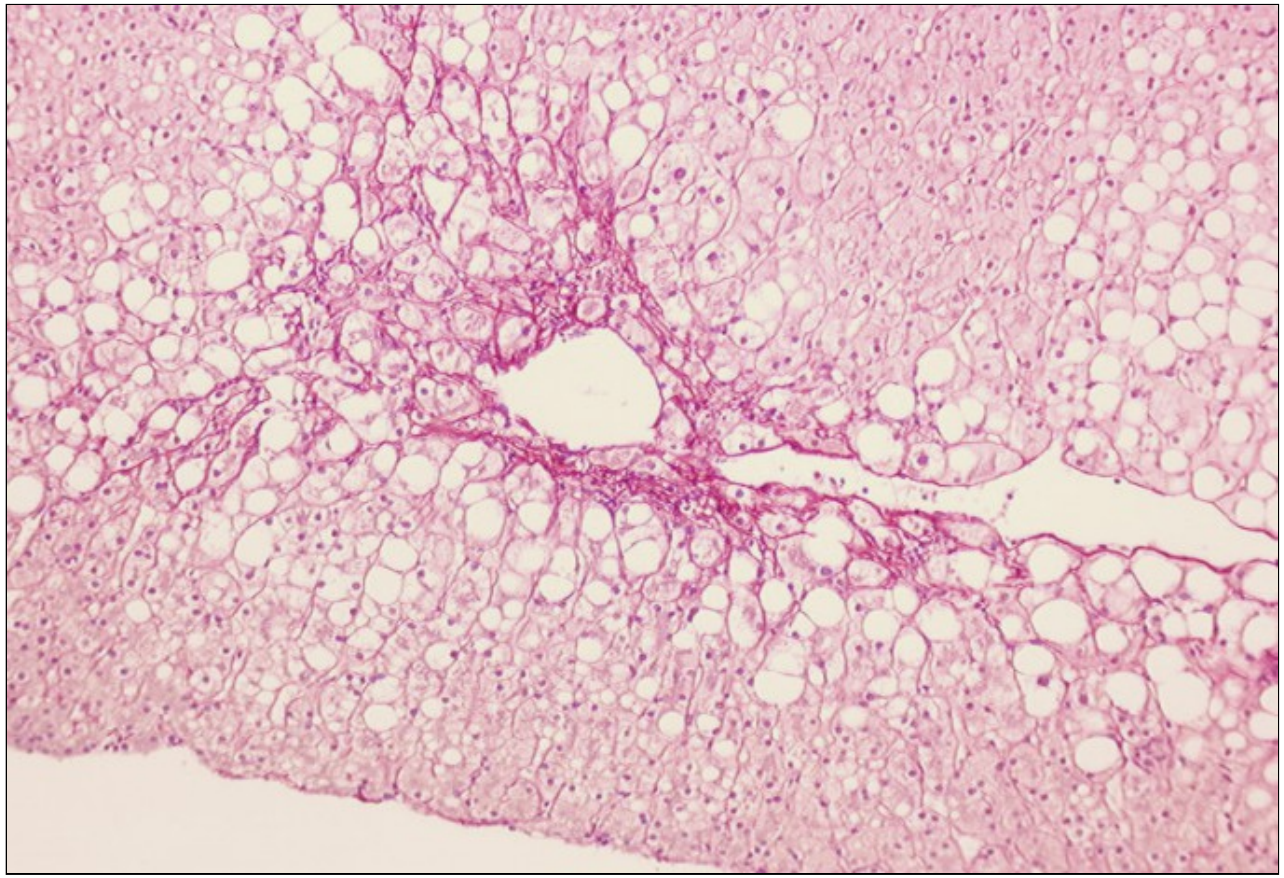


NAFLD

FIBROSIS IN CHRONIC HEPATITIS

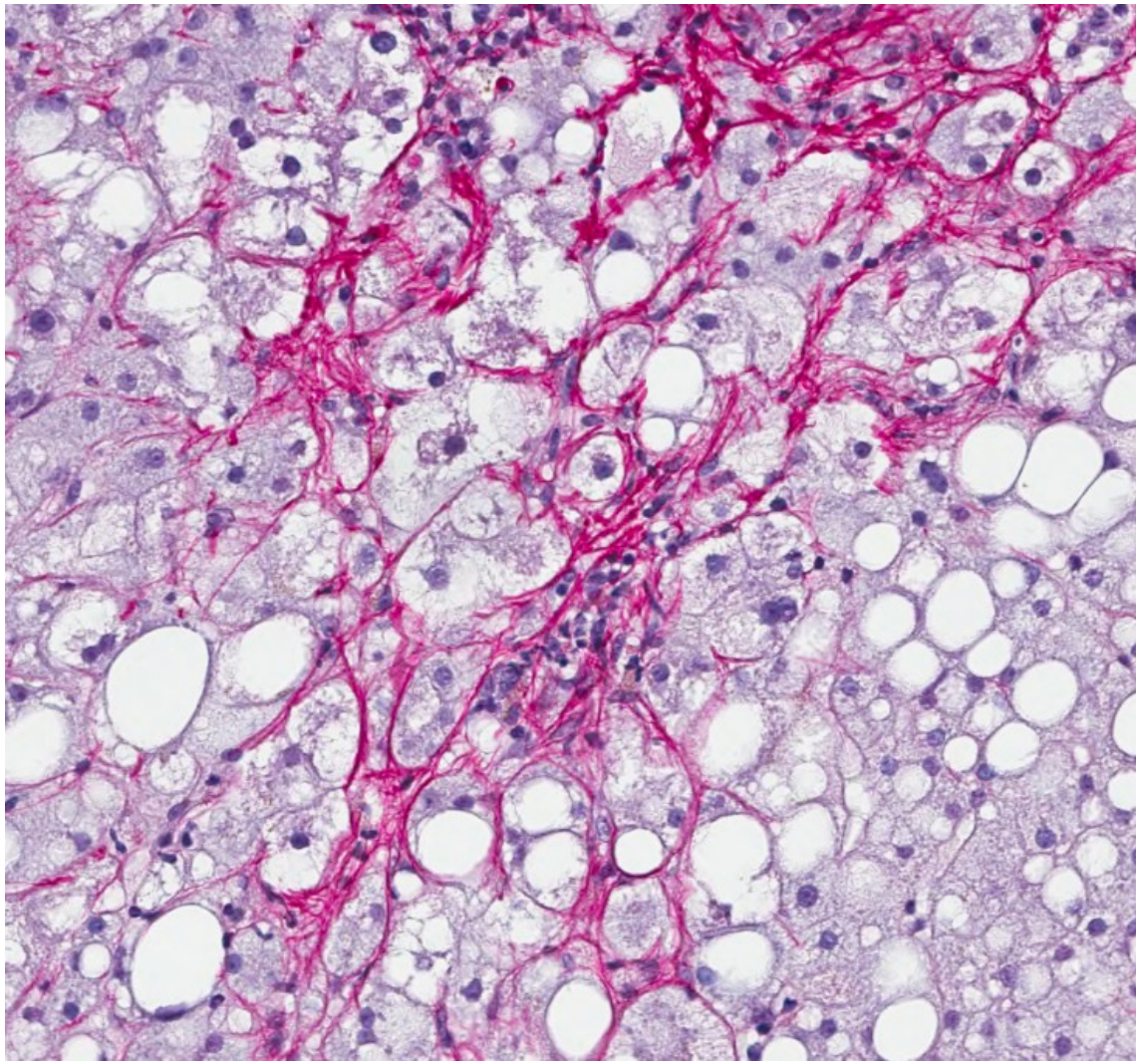


SPECIFITY OF FIBROSIS IN NAFLD



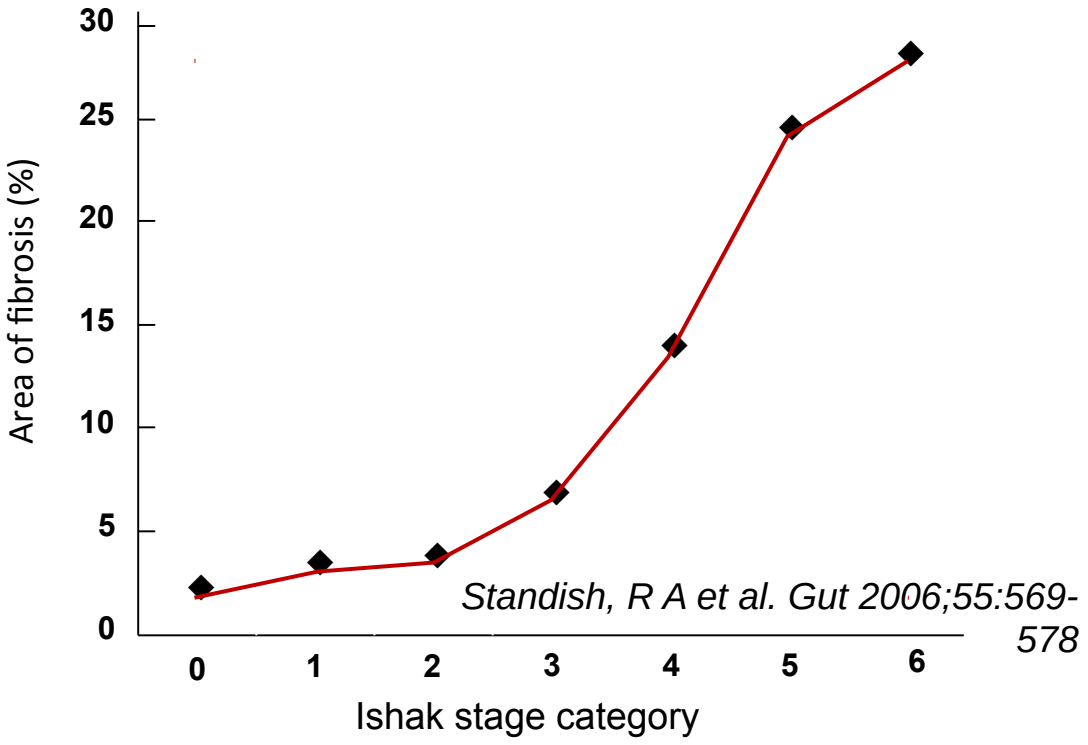
PERICENTRAL FIBROSIS

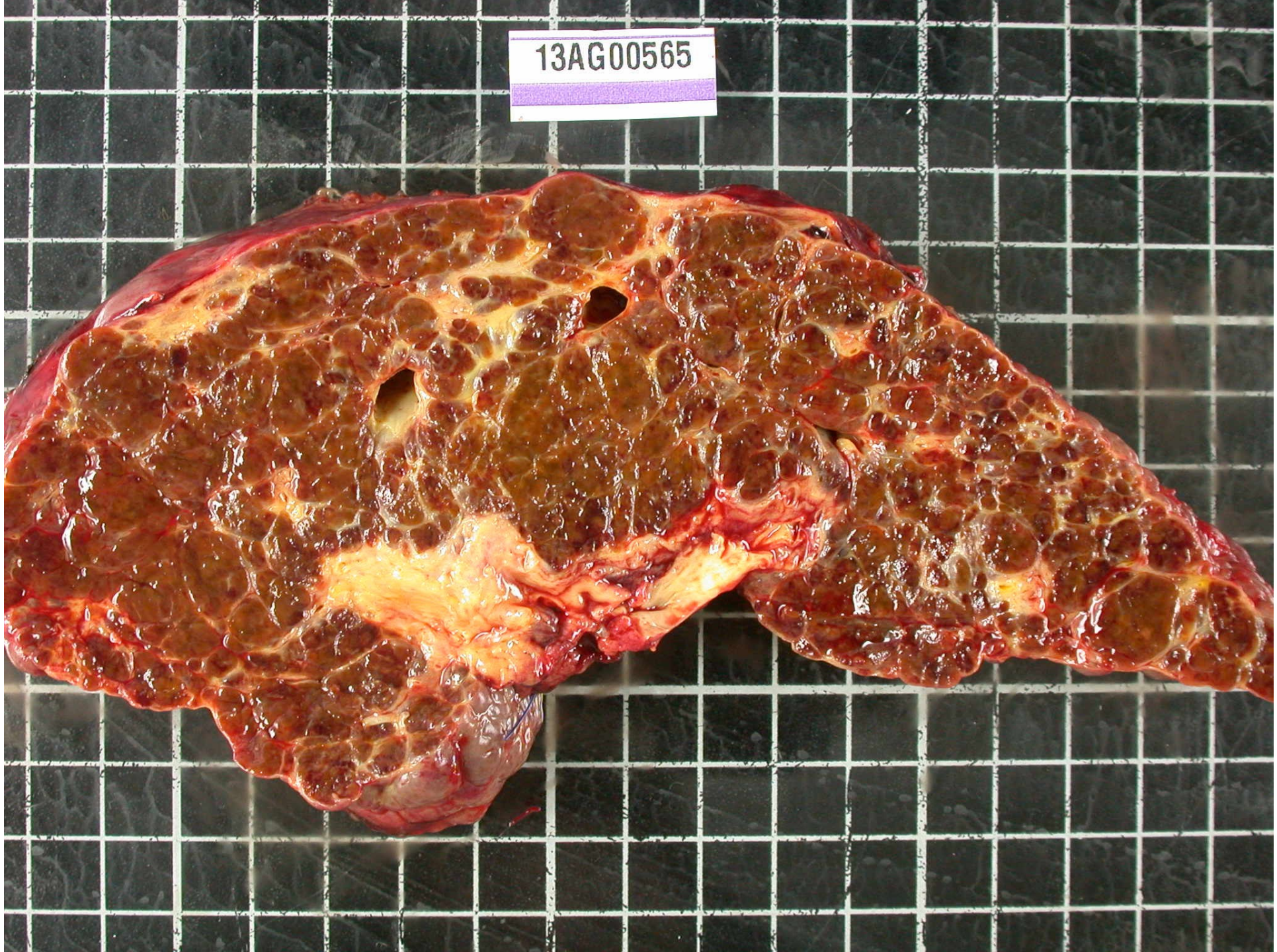
PERISINUSOIDAL FIBROSIS



Comment 2 : AMOUNT OF FIBROSIS DIFFERENT FROM STAGE OF FIBROSIS

Amount of fibrosis (morphometry) and histological stage

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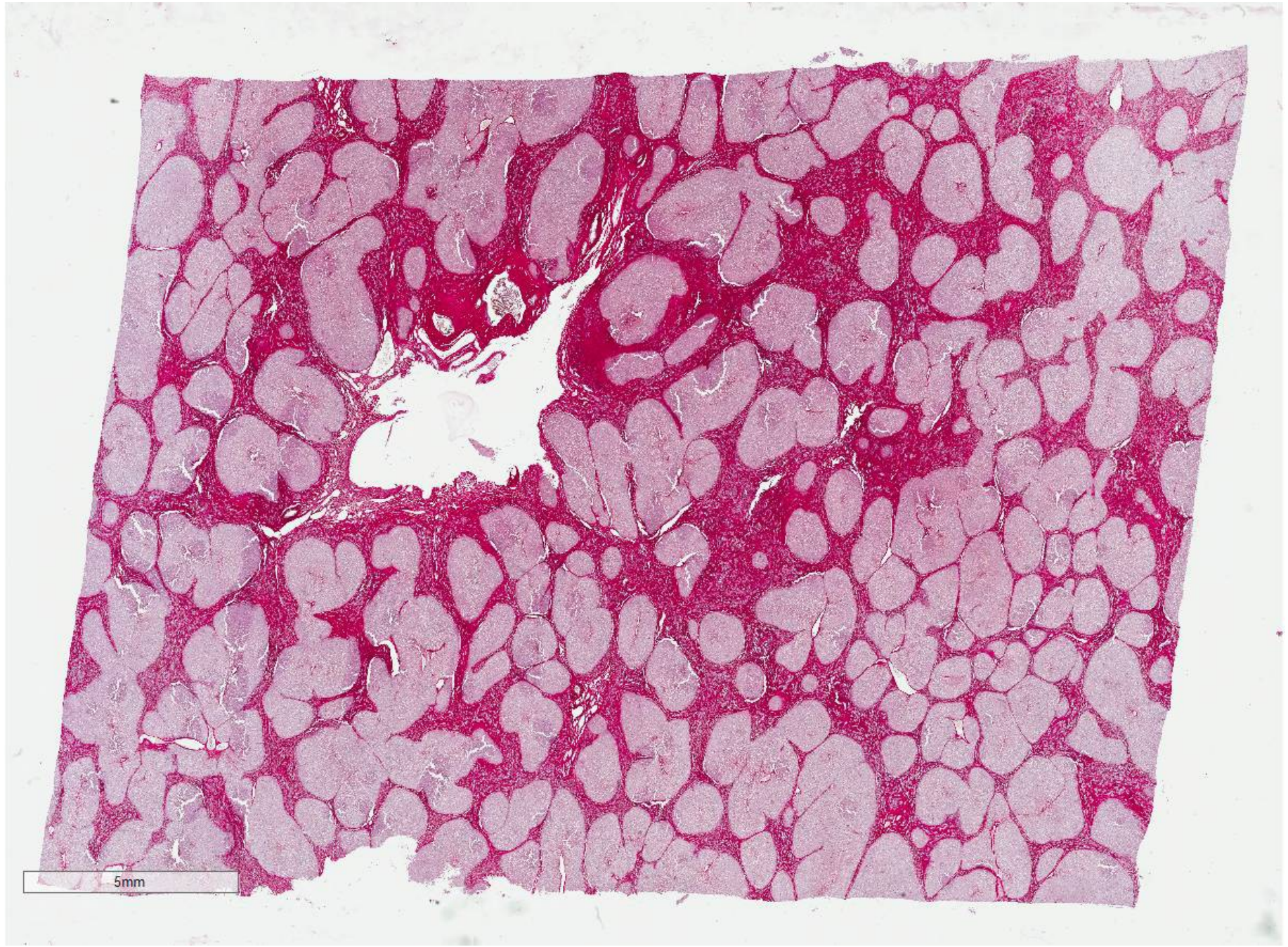
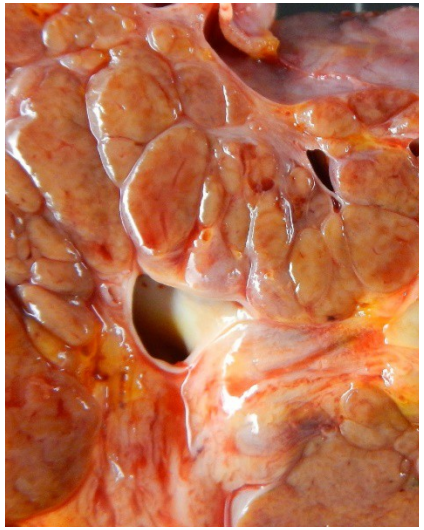

5mm

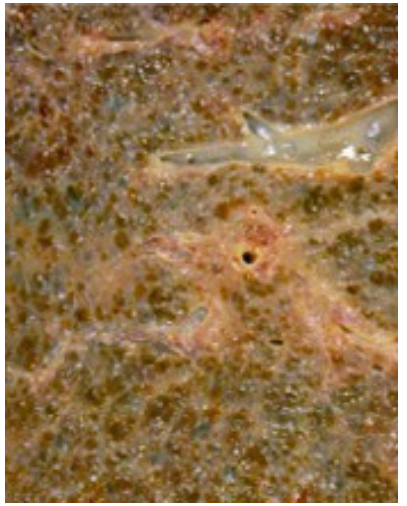
COMMENT 3 : ALL CIRRHOSIS ARE NOT ALIKE - A DISEASE WITH A WIDE SPECTRUM

Histological	F1-F3		F4 (Cirrhosis)	
Clinical	*Non-cirrhotic*	*Compensated*	*Compensated*	*Decompensated*
Symptoms	None	None (no varices)	None (varices present)	Ascites, VH, Encephalopathy
Sub-stage	-	Stage 1	Stage 2	Stages 3 and 4
Hemodynamic		>6	>10	>12



4a

4b



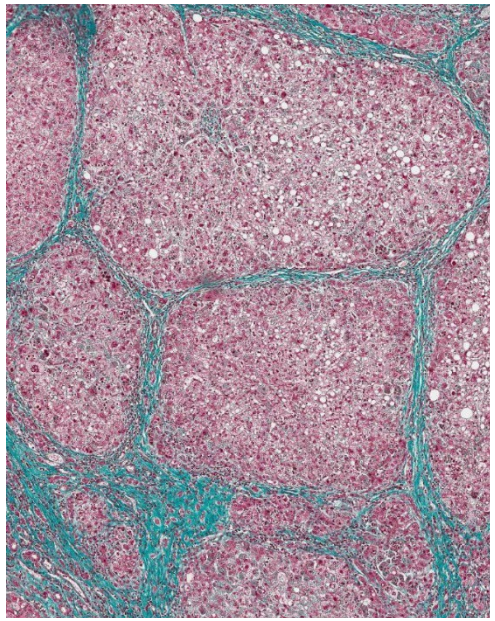
4c

Garcia-Tsao G, et al. Now there are many (stages) where before there was one: in search of a pathophysiological classification of cirrhosis. Hepatology 2010; 51: 1445–9

SU Kim, et al. The Laennec staging system for histological sub-classification of cirrhosis is useful for stratification of prognosis in patients with liver cirrhosis. J Hepatol 2012

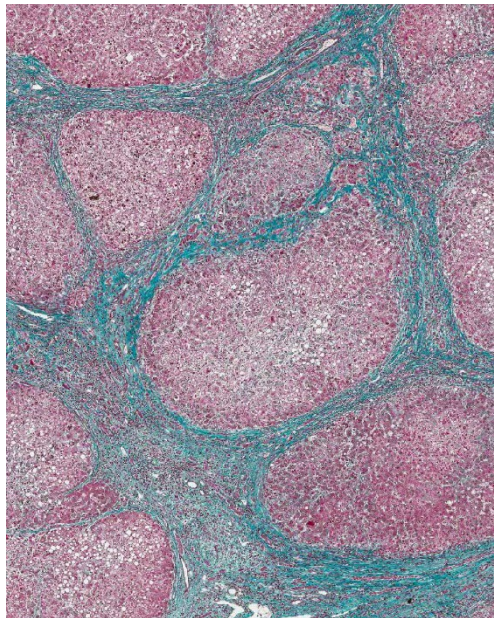
LAENNEC SCORING SYSTEM OF CIRRHOSIS

4a



- Thin fibrous septa
- Regenerative nodules

4b



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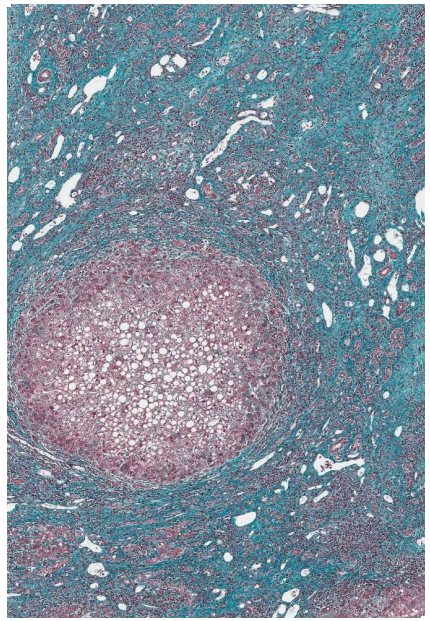
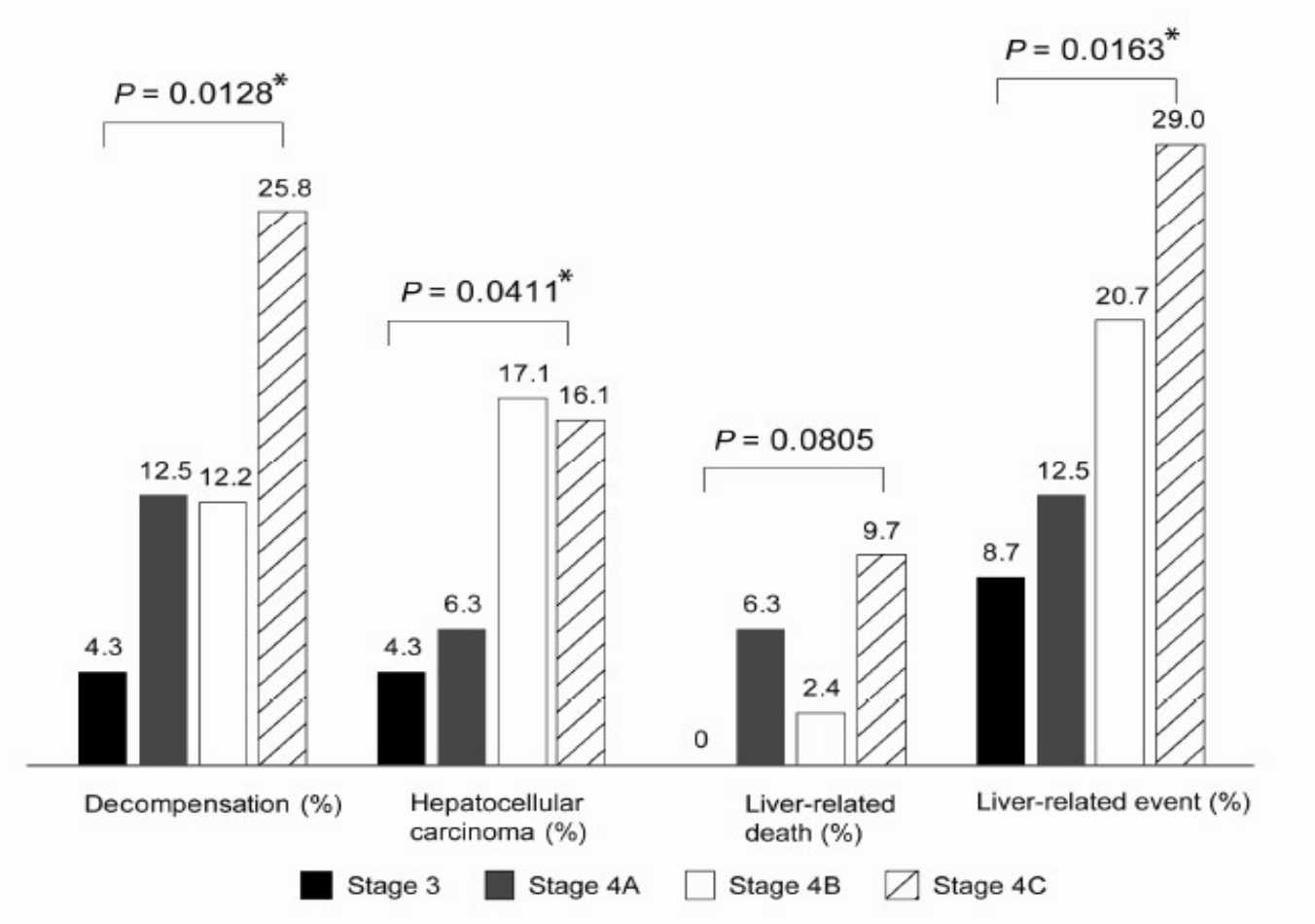


- Thick fibrous septa
- Atrophic nodules

- The Laennec staging system for histological sub-classification of cirrhosis is useful for stratification of prognosis in patients with liver cirrhosis SU Kim, HJ Oh, IR. Wanless, S Lee, YN Park, J Hepatol 2012
- Cirrhosis histology and Laennec staging system correlate with high portal pressure. Rastogi A, Maiwall R, Bihari C, Ahuja A, Kumar A, Singh T, Wani ZA, Sarin SK. Histopathology 2012

Clinical relevance of scoring cirrhosis



The Laennec staging system for histological sub-classification of cirrhosis is useful for stratification of prognosis in patients with liver cirrhosis SU Kim, HJ Oh, IR. Wanless, S Lee, YN Park, J Hepatol 2012

Comment 4 : Cirrhosis may regression after antiviral treatment.

Impact of Pegylated Interferon Alfa-2b and Ribavirin on Liver Fibrosis in Patients With Chronic Hepatitis C

THIERRY POYNARD,* JOHN McHUTCHISON,† MICHAEL MANNS,§ CHRISTIAN TREPO,‖ KAREN LINDSAY,¶ ZACHARY GOODMAN,# MEI–HSIU LING,** and JANICE ALBRECHT** for the PEG-FIBROSIS Project Group

*Service d'Hépato-Gastroentérologie, Groupe Hospitalier Pitié-Salpêtrière, Université Paris VI, Paris, France; †Scripps Clinic and Research Foundation, Division of Gastroenterology/Hepatology, La Jolla, California; §Division of Gastroenterology and Hepatology, Medical School of Hannover, Hannover, Germany; ‖Service d'Hépato-Gastroentérologie, Hôtel Dieu, Lyon, France; ¶Division of Gastrointestinal and Liver Disease, University of Southern California, Los Angeles, California; #Department of Hepatic and Gastrointestinal Pathology, Armed Forces Institute of Pathology, Washington, DC; and **Schering-Plough Research Institute, Kenilworth, New Jersey

GASTROENTEROLOGY 2002;122:1303–1313

See editorial on page 1525.

Background & Aims: **Liver fibrosis is an important prognostic factor in patients with hepatitis C. The effect of pegylated (PEG) interferon alone or its combination with ribavirin on fibrosis has not been established.** ***Methods:*** **We pooled individual data from 3010 naive patients with pretreatment and posttreatment biopsies from 4 randomized trials. Ten different regimens combining standard interferon, PEG interferon, and ribavirin were compared. The impact of each regimen was estimated by the percentage of patients with at least 1 grade improvement in the necrosis and inflammation (METAVIR score), the percentage of patients with at least 1 stage worsening in fibrosis METAVIR score, and by the fibrosis progression rate per year.** ***Results:*** **Necrosis and inflammation improvement ranged from 39% (interferon 24 weeks) to 73% (optimized PEG 1.5 and ribavirin; $P < 0.001$). Fibrosis worsening ranges from 23% (interferon 24 weeks) to 8% (optimized PEG 1.5 and ribavirin; $P < 0.001$). All regimens significantly reduced the fibrosis progression rates in comparison to rates before treatment. The reversal of cirrhosis was observed in 75 patients (49%) of 153 patients with baseline cirrhosis. Six factors were independently associated with the absence of significant fibrosis after treatment: baseline fibrosis stage (odds [OR] = 0.12; $P <$ 0.0001), sustained viral re (OR = 0.36; $P <$**

atitis C involves the gradual progression of hepatic fibrosis that can eventually lead to cirrhosis. Most of the complications related to chronic infection occurs in patients who have established cirrhosis.[3–5] Treatments that could halt or diminish the progression of fibrosis would theoretically be beneficial.[6]

We have previously reported that the combination regimen of interferon and ribavirin slows progression of liver fibrosis and even leads to regression in a proportion of patients. The impact on fibrosis was related both to the response to therapy and the duration of interferon treatment.[7]

Recently, it has been shown that the pegylated form of interferon (PEG-interferon) has a significantly higher efficacy in achieving sustained response in comparison to standard interferon. This greater efficacy has been observed both for monotherapy[8–10] or in combination with ribavirin.[11] The effect of these new regimens on histological changes has not been well characterized.[8–11]

The aim of this study was to compare the efficacy of these different regimens (PEG-interferon alone or in combination with ribavirin) on fibrosis progression and on the necrosis and inflammatory features and to identify risk factors for these changes. This analysis was undertaken to determine the impact of therapy in patients who eradicate the virus, and also in patients who do not

The reversal of cirrhosis was observed in 75 patients **(49%)** of 153 patients with baseline cirrhosis

Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study

Patrick Marcellin, Edward Gane, Maria Buti, Nezam Afdhal, William Sievert, Ira M Jacobson, Mary Kay Washington, George Germanidis, John F Flaherty, Raul Aguilar Schall, Jeffrey D Bornstein, Kathryn M Kitrinos, G Mani Subramanian, John G McHutchison, E Jenny Heathcote

Lancet 2013; 381: 468–75
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See Comment page 433

Service d'Hépatologie, Hôpital Beaujon, and INSERM Unit CRB3, Clichy, France (Prof P Marcellin MD); Auckland City Hospital, Auckland, New Zealand (Prof E Gane MD); Liver Unit, Hospital General Universitari Vall d'Hebron and CIBERehd, Barcelona, Spain (Prof M Buti MD); Division of Gastroenterology, Beth Israel Deaconess Medical Center, Boston, MA, USA (Prof N Afdhal MD); Monash University and Monash Medical Centre, Melbourne, VIC, Australia (Prof W Sievert MD); Weill Cornell Medical College, New York, NY, USA

Summary

Background Whether long-term suppression of replication of hepatitis B virus (HBV) has any beneficial effect on regression of advanced liver fibrosis associated with chronic HBV infection remains unclear. We aimed to assess the effects on fibrosis and cirrhosis of at least 5 years' treatment with tenofovir disoproxil fumarate (DF) in chronic HBV infection.

Methods After 48 weeks of randomised double-blind comparison (trials NCT00117676 and NCT00116805) of tenofovir DF with adefovir dipivoxil, participants (positive or negative for HBeAg) were eligible to enter a 7-year study of open-label tenofovir DF treatment, with a pre-specified repeat liver biopsy at week 240. We assessed histological improvement (≥2 point reduction in Knodell necroinflammatory score with no worsening of fibrosis) and regression of fibrosis (≥1 unit decrease by Ishak scoring system).

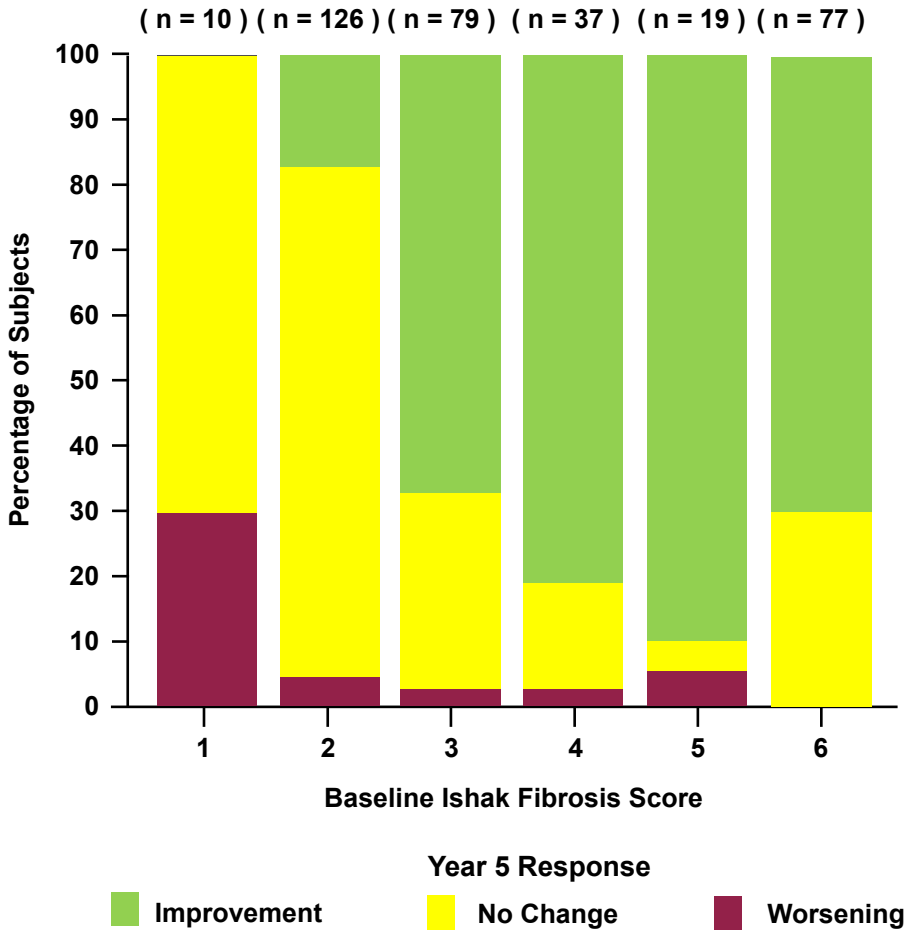
Findings Of 641 patients who received randomised treatment, 585 (91%) entered the open-label phase, and 489 (76%) completed 240 weeks. 348 patients (54%) had biopsy results at both baseline and week 240. 304 (87%) of the 348 had histological improvement, and 176 (51%) had regression of fibrosis at week 240 ($p<0·0001$). Of the 96 (28%) patients with cirrhosis (Ishak score 5 or 6) at baseline, 71 (74%) no longer had cirrhosis (≥1 unit decrease in score), whereas three of 252 patients without cirrhosis at baseline progressed to cirrhosis at year 5 ($p<0·0001$). V[illegible]logical breakthrough occurred infrequently and was not due to resistance to tenofovir DF. The safety profile w[illegible]favourable: 91 (16%) patients had adverse events but only nine patients had serious events related to the study dr[illegible]

Interpretation In patients with chronic HBV infection, up to 5 years of treatment with t[illegible] DF was safe and effective. Long-term suppression of HBV can lead to regression of fibrosis and cirrhosis.

Of the 96 (28%) patients with cirrhosis (Ishak score 5 or 6) at baseline, 71 **(74%)** no longer had cirrhosis

Histological outcome of Hepatitis B during long-term Tenofovir treatment

- 5 year treatment with tenofovir DF in HBeAg-ve and +ve patients
- 348 patients with paired biopsies before treatment, at Year 1 and Year 5
- **96% of patients with paired biopsies either improved fibrosis score or did not change at year 5**
- Cirrhosis regression (Ishak score ≥5) occurred in 74% of patients with cirrhosis at baseline

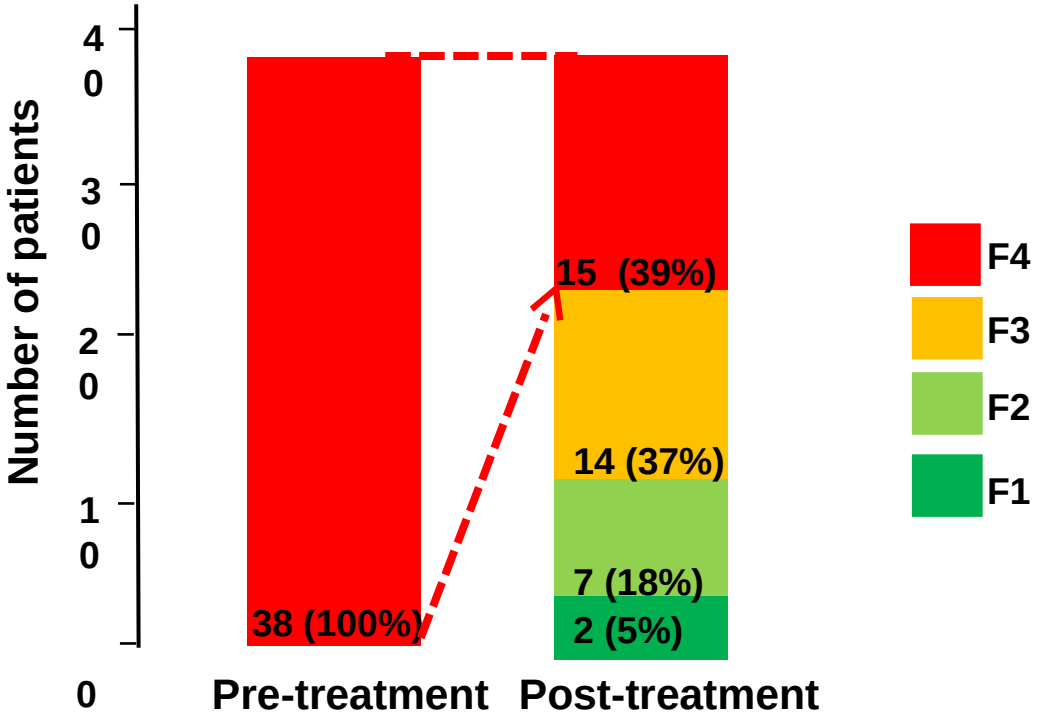


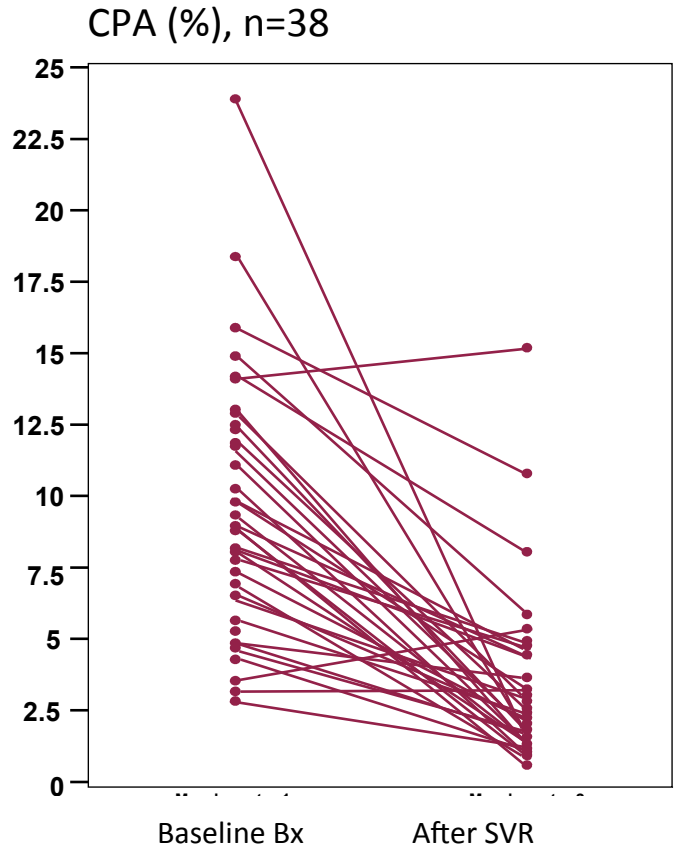
1. Marcellin P, *et al*. AASLD 2011; Poster #1375

Outcome of Metavir fibrosis stage in liver biopsies after SVR in cirrhosis C

D'Ambrosio *et al* *Hepatology.* 2012

- 38 patients, Cirrhosis C, Child-Pugh A - 24/48 weeks standard bitherapy and SVR
- Paired biopsy, mean interval : 6 years, mean length 25mm

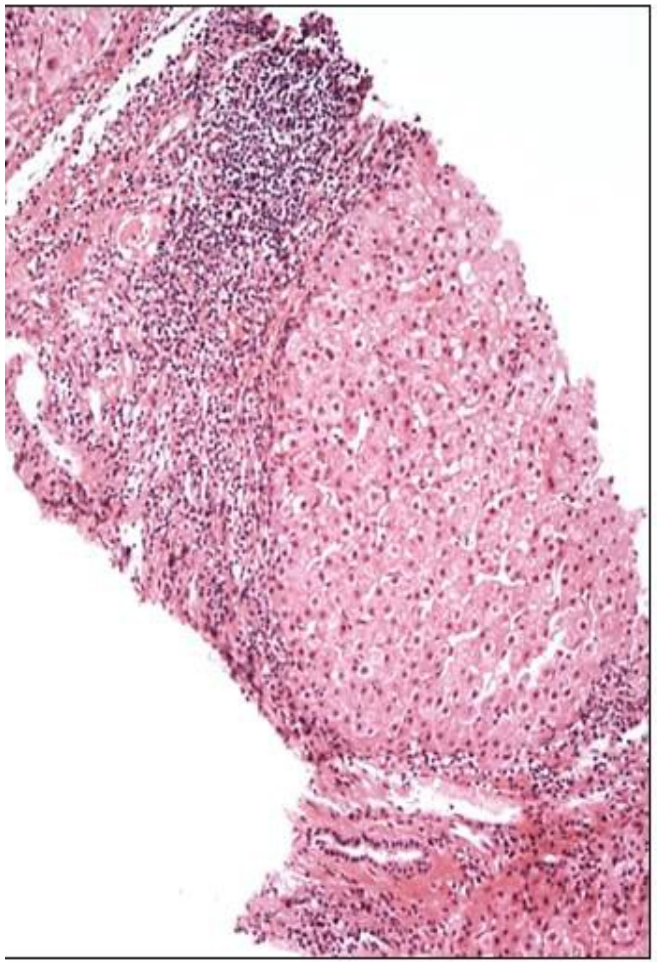




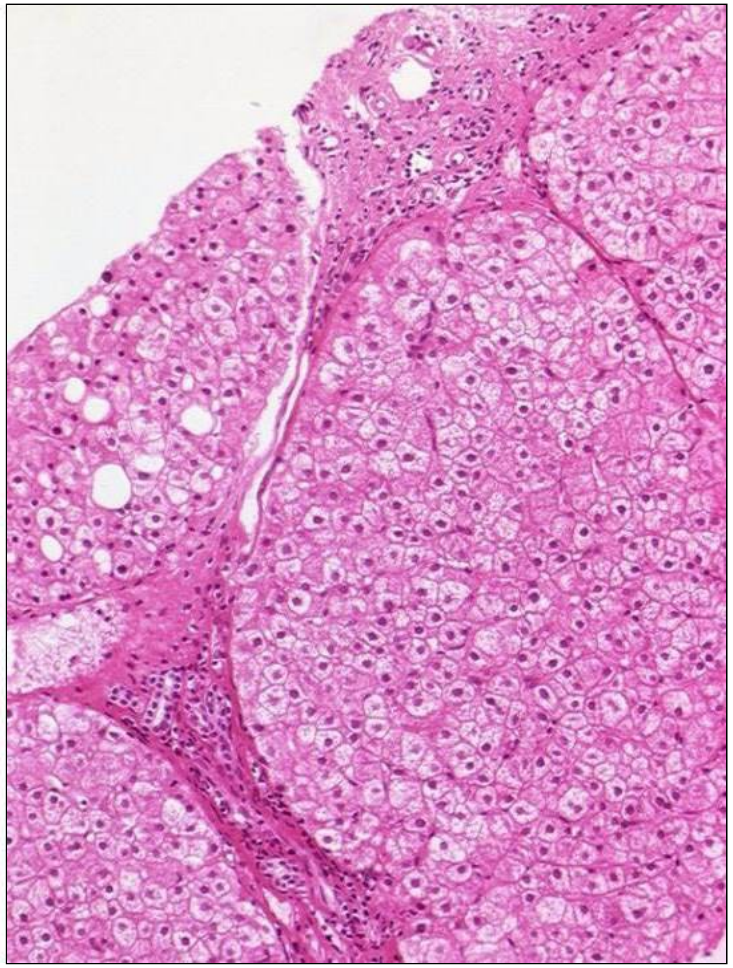
61% patients with F4 at baseline had cirrhosis regression to lower METAVIR stages

CIRRHOSIS C

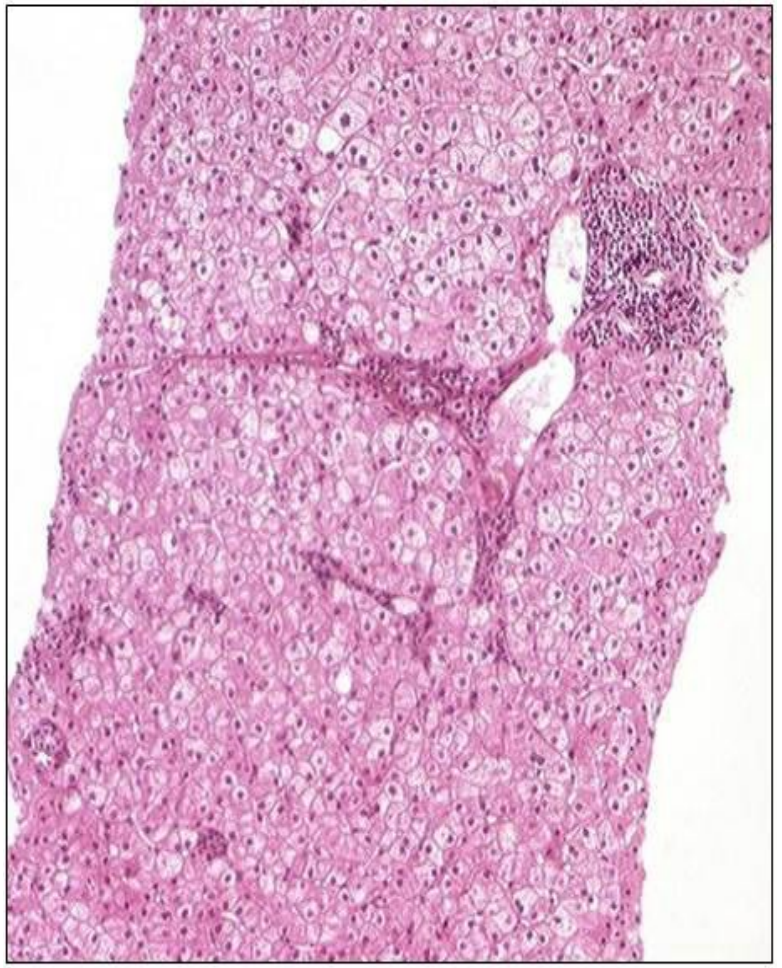
PRETREATMENT BIOPSY



3 years AFTER SVR



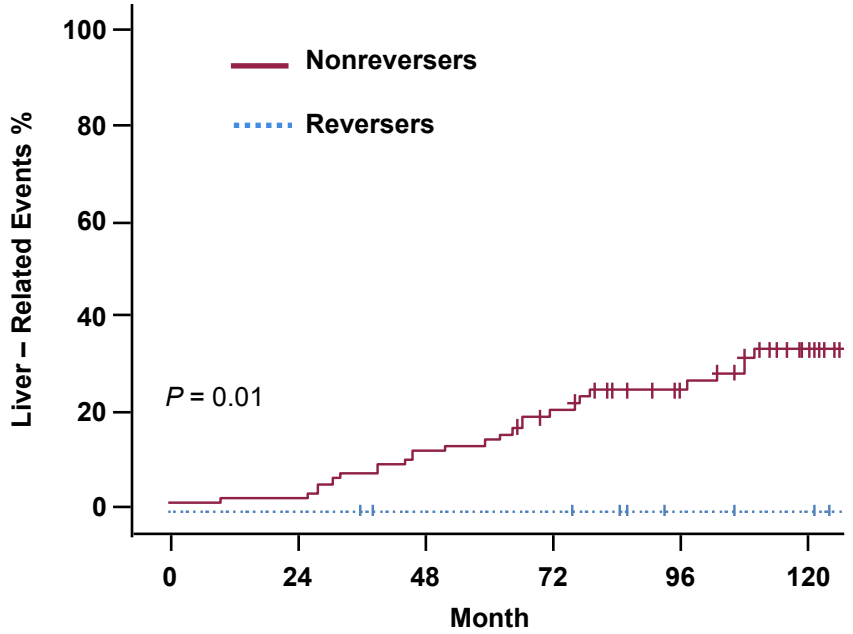
6 years AFTER SVR



D'Ambrosio R, Aghemo A, Rumi MG, Ronchi G, Donato MF, Paradis V, Colombo M, Bedossa P. A morphometric and immunohistochemical study to assess the benefit of a sustained virological response in hepatitis C virus patients with cirrhosis. Hepatology. 2012 Aug;56(2):532-43.

The relationship of regression of cirrhosis to clinical outcome in Hep C

- 96 patients with biopsy-proven Hep C cirrhosis treated with an Ifn-based regimen and post-treatment liver biopsy (median follow-up: 118 months)
- 18 patients had regression of cirrhosis.
- The incidence of LRE was 0 per 100 patient/years in patients with regression of cirrhosis and 4 in patients without regression of cirrhosis
- The transplantation-free survival rate at 10 years was 100% in patients with regression of cirrhosis and 74.2% in patients without regression of cirrhosis



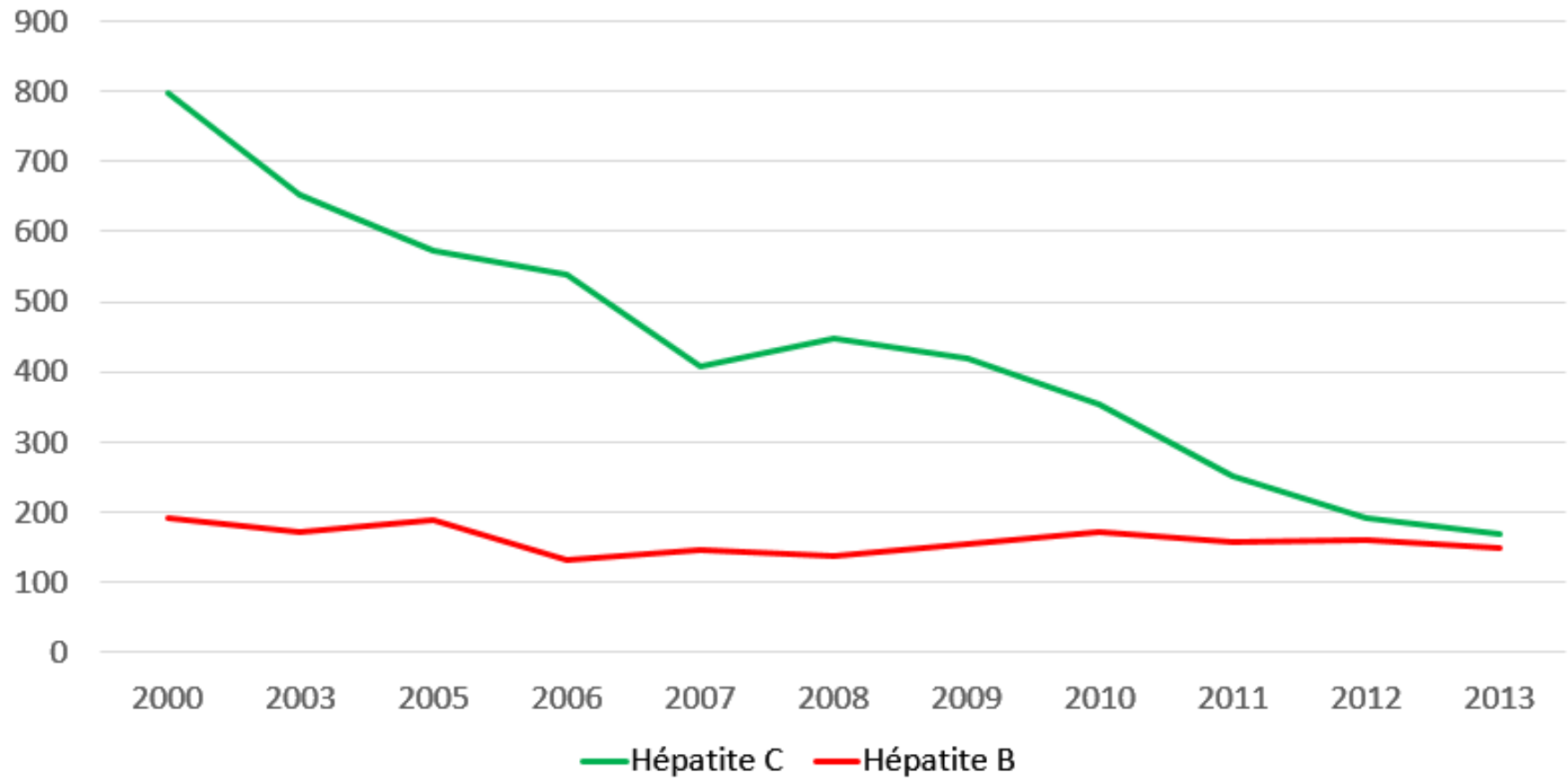
Liver-related events" were hepatocellular carcinoma, hepatic encephalopathy, variceal bleeding, ascites, spontaneous bacterial peritonitis, and liver transplantation.

Adapted from Mallet V, *et al. Ann Intern Med* 2008; 149:399-403

Regression of cirrhosis is associated with decreased Liver-related morbidity and improved survival

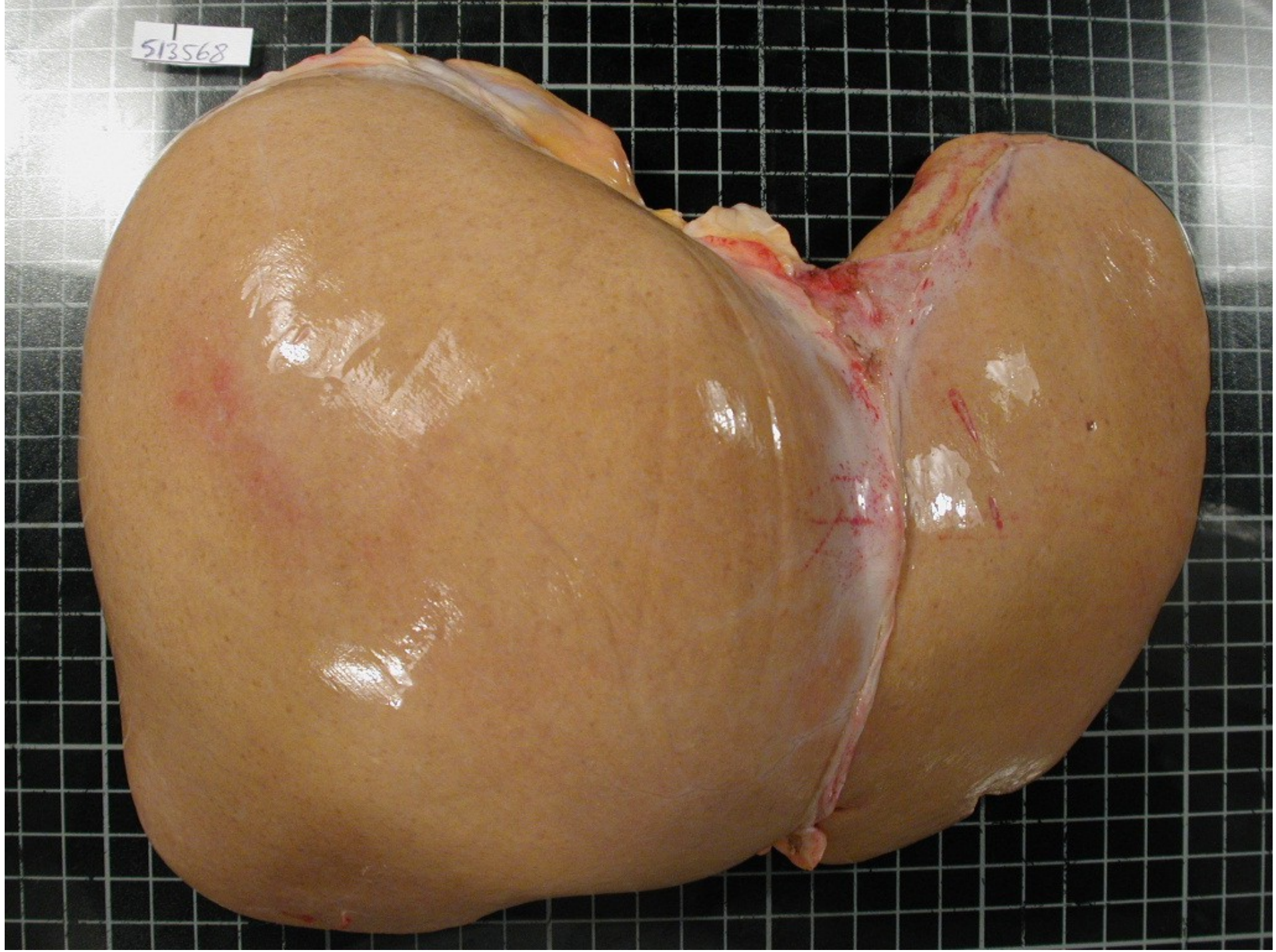
Mallet V, *et al. Ann Intern Med* 2008; 149:399-403

Number of liver biopsy per year from 2000 to 2013 for chronic viral hepatitis in Beaujon hospial



FIBROSIS : questions from the pathologist ?

- Different type of fibrosis: one single or several different tools ?
- Can we assess the different stages of cirrhosis uninvasively ?
- Fibrosis regression: how to evaluate it non invasively ?
- Given the low accuracy of NI tools to differentiate between intermediate stages of fibrosis (F1vsF2 or F2vsF3), is it realistic to rely on staging fibrosis with these NI tools in antiviral treatment guidelines.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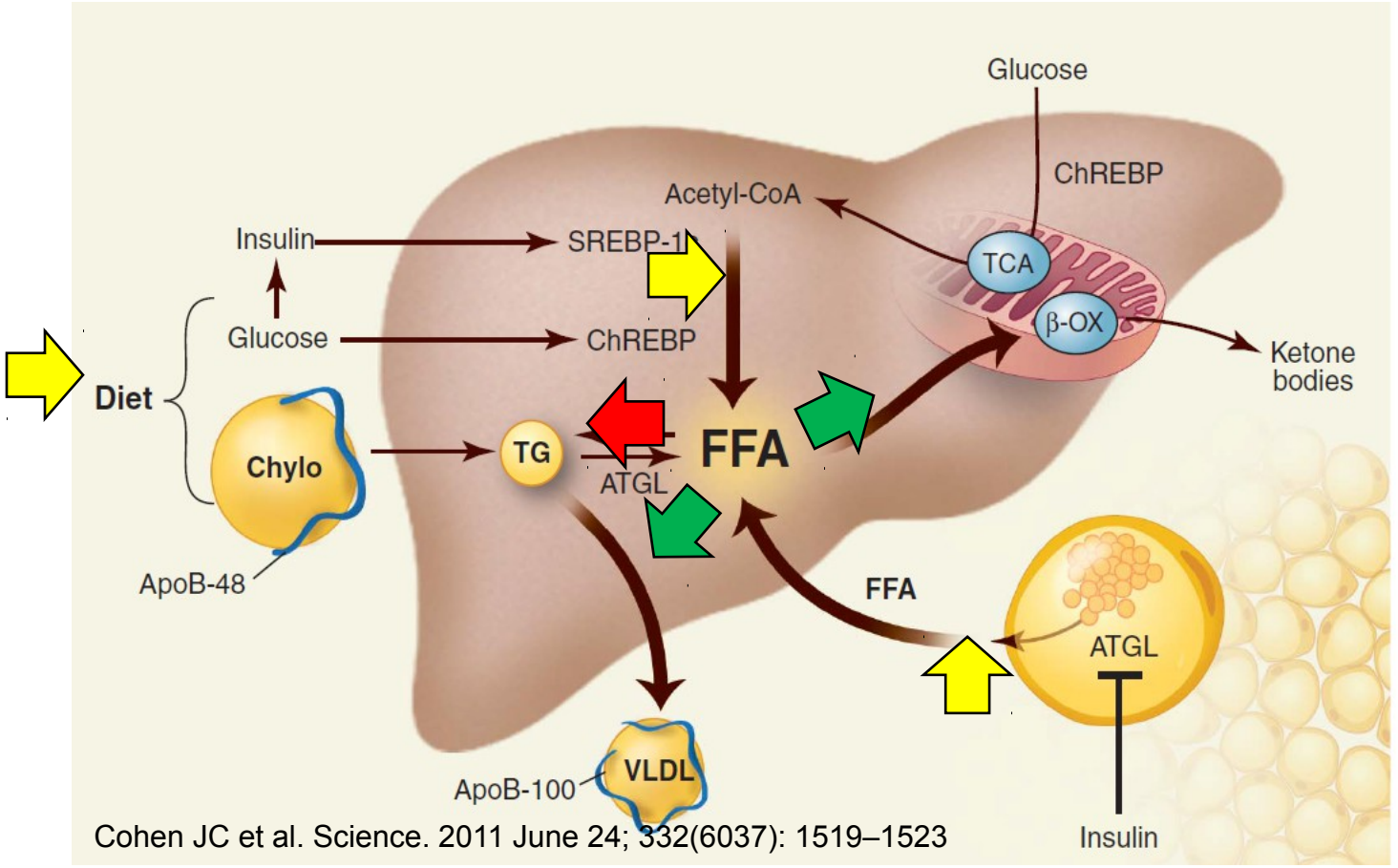
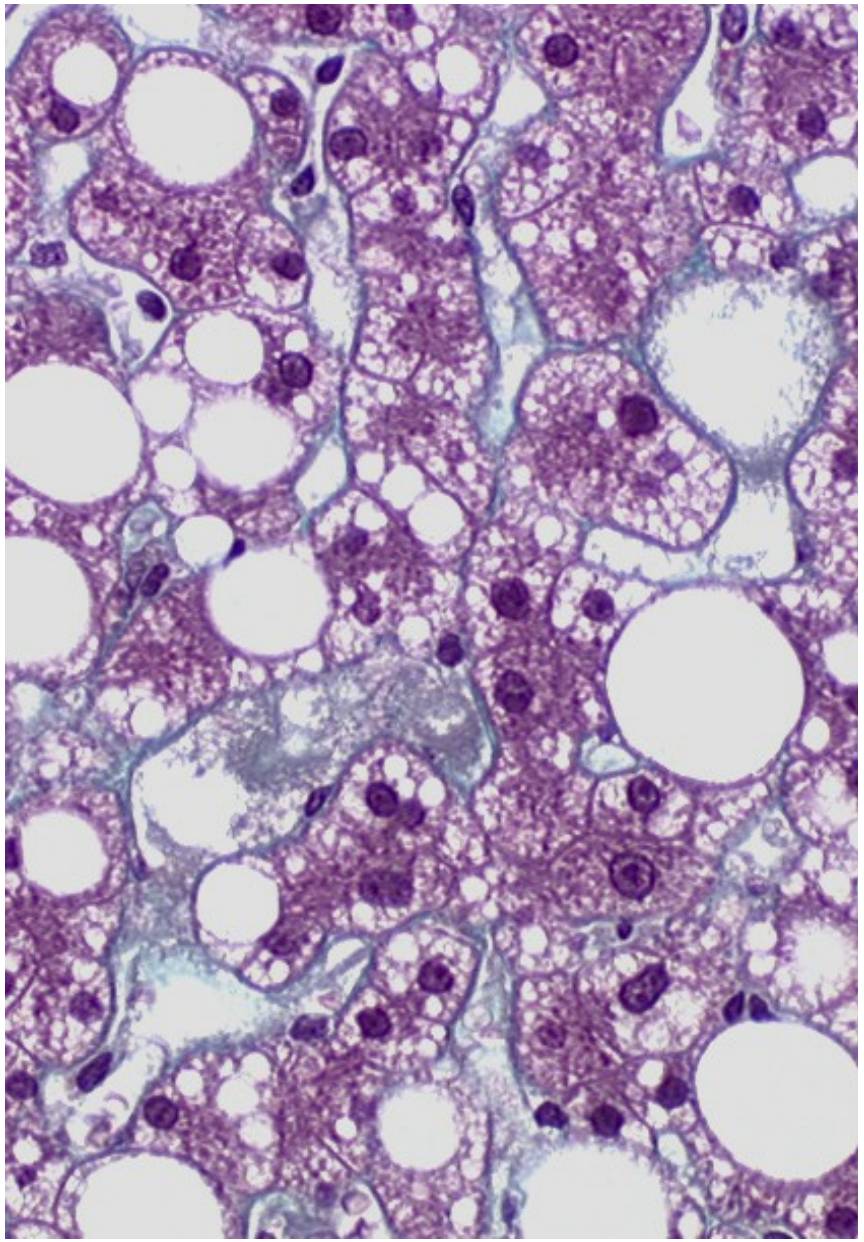
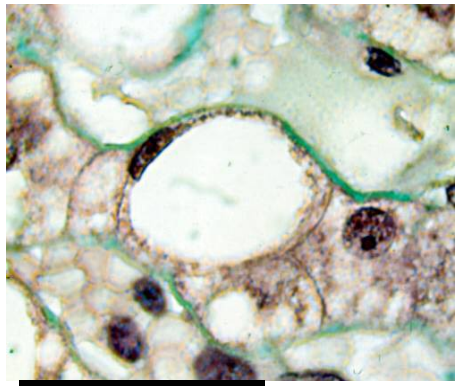
Hepatic metabolism of Free Fatty Acid

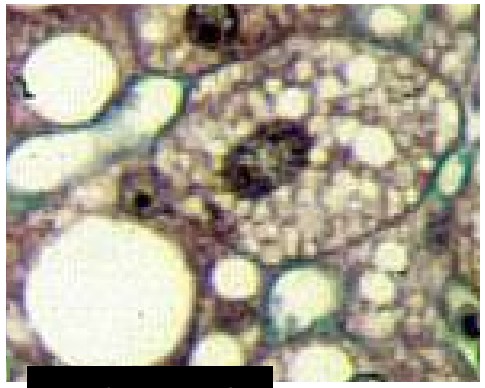


Cohen JC et al. Science. 2011 June 24; 332(6037): 1519–1523

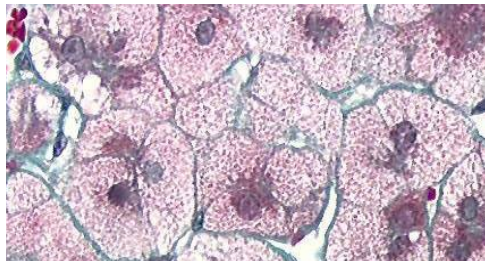




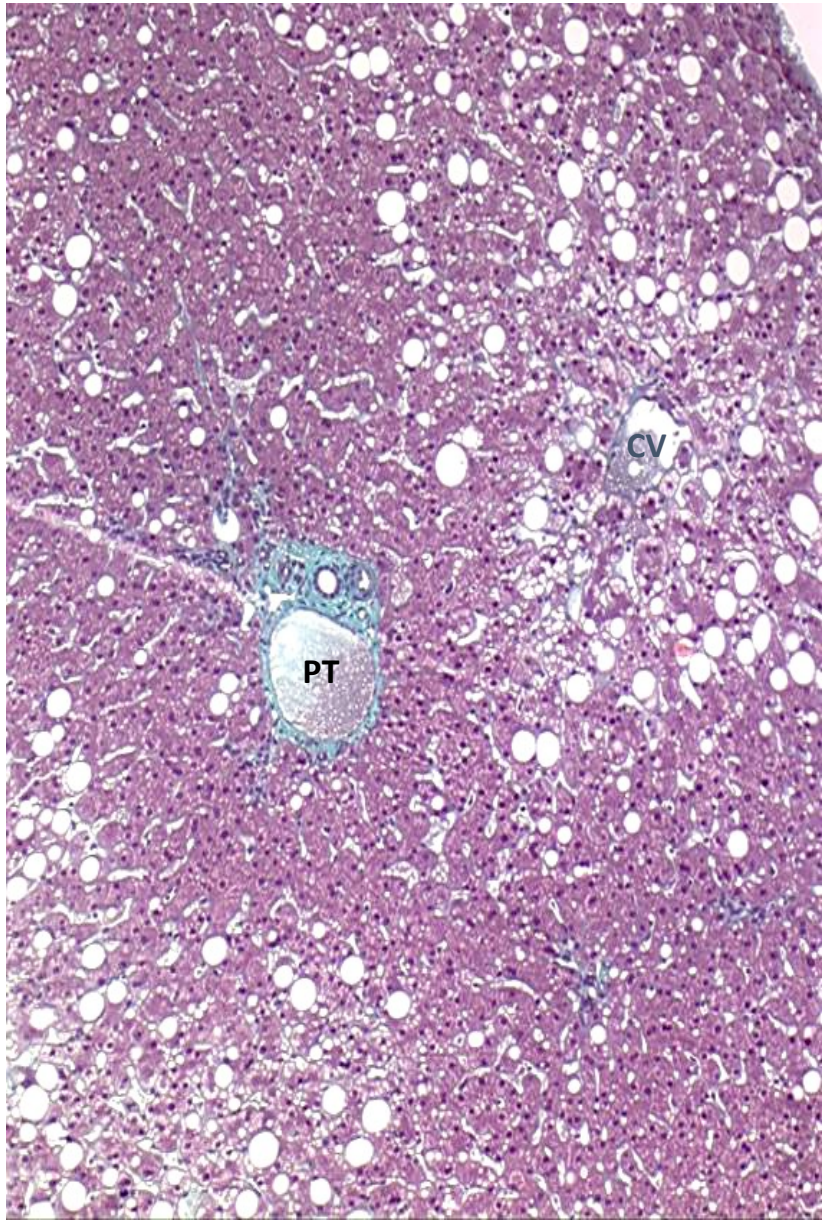
Macrovacuole



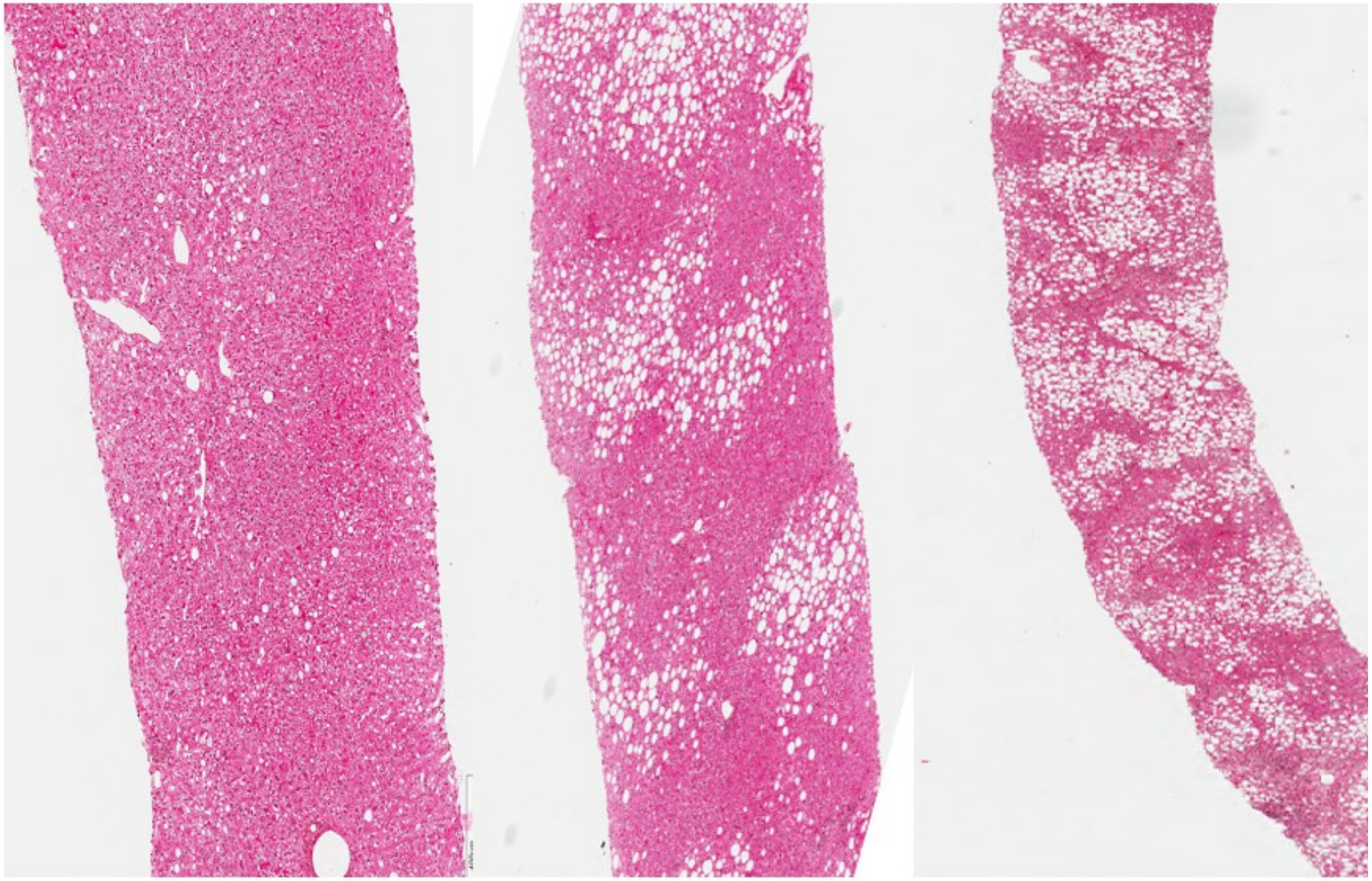
Mediovacuole



Microvacuole (rare)

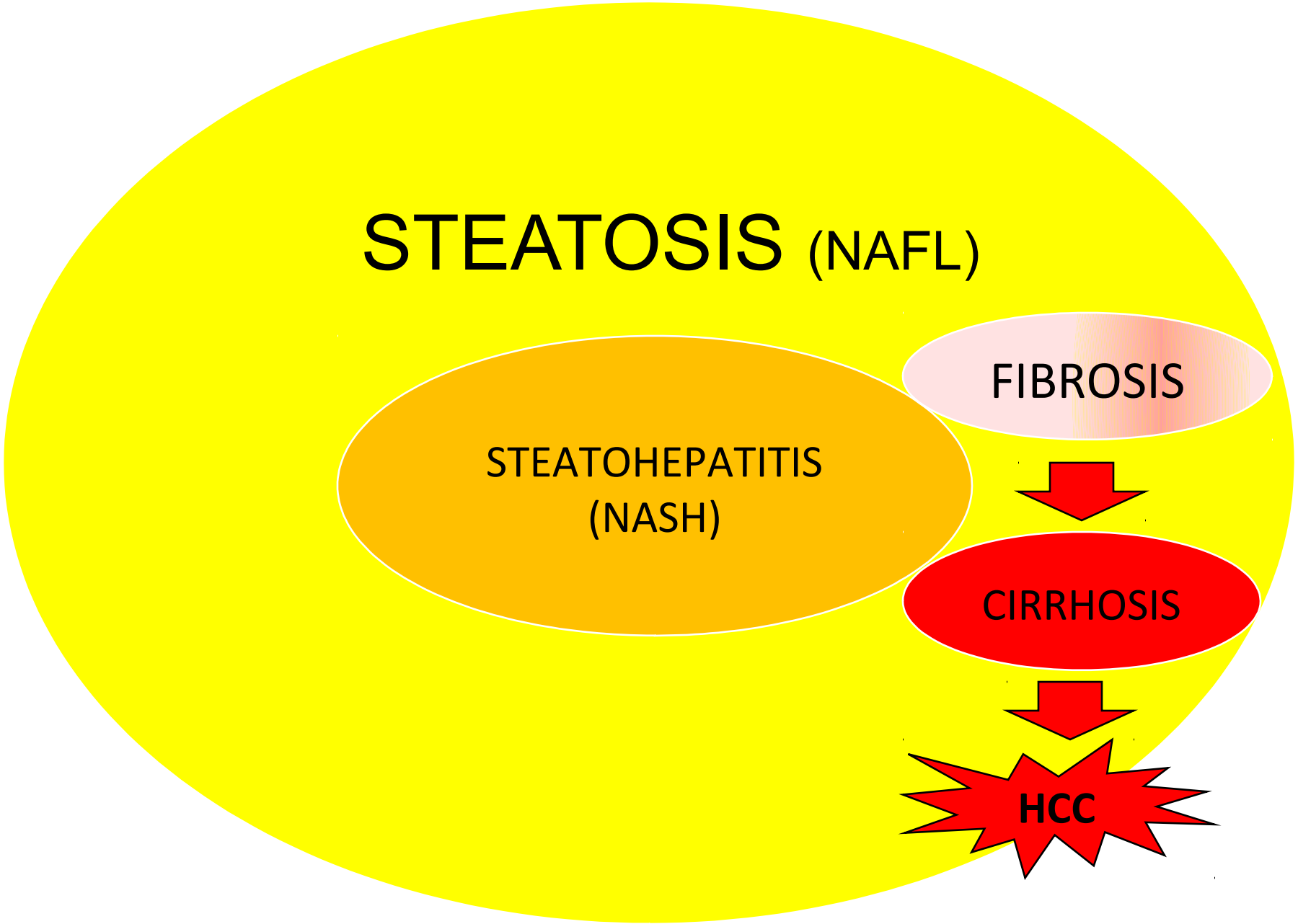


- **S**teatosis (0-3) 0 = <5%, 1 = 5-33%, 2 = 34-66%, 3 = >66%

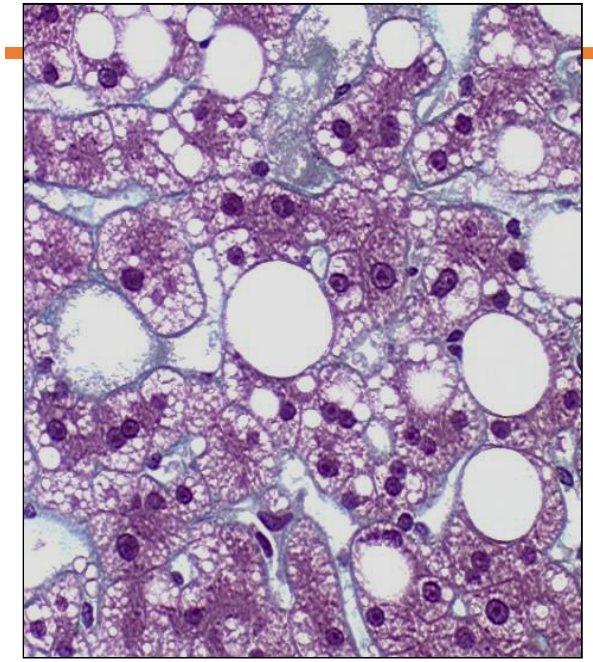


S1 S2 S3

NAFLD : a spectrum of histological patterns



Non Alcoholic Steatohepatitis (NASH)



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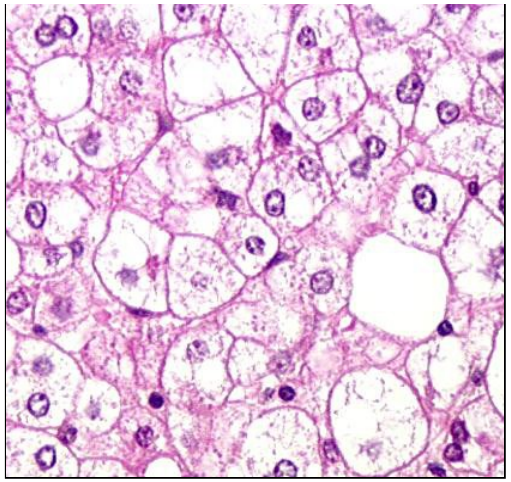
Inflammation lobulaire



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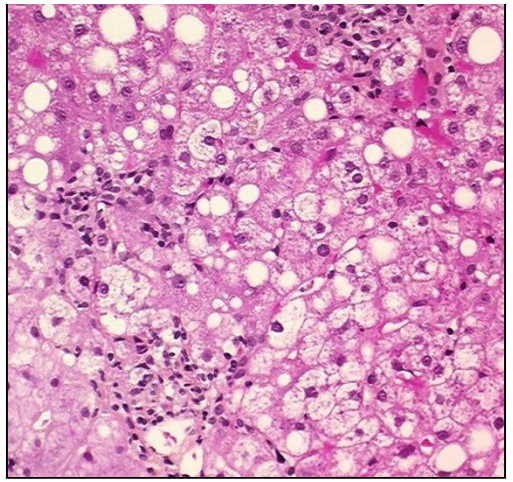
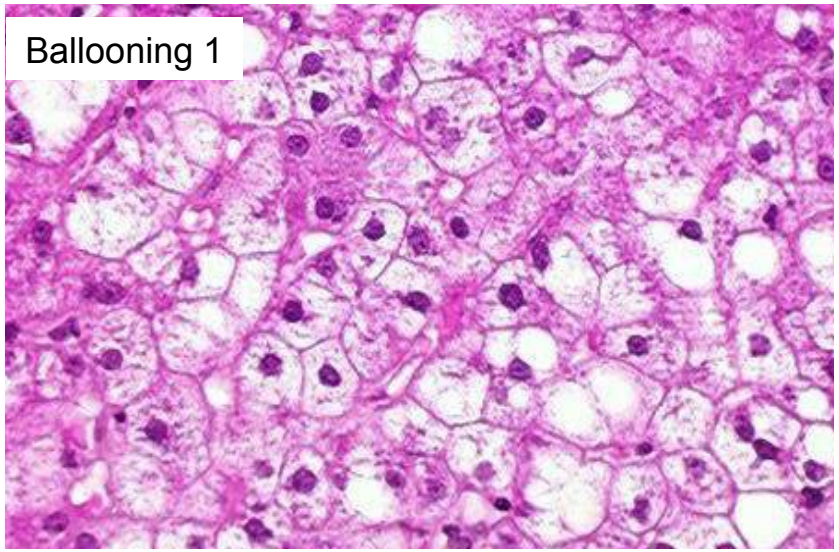
Ballonisation/clarification

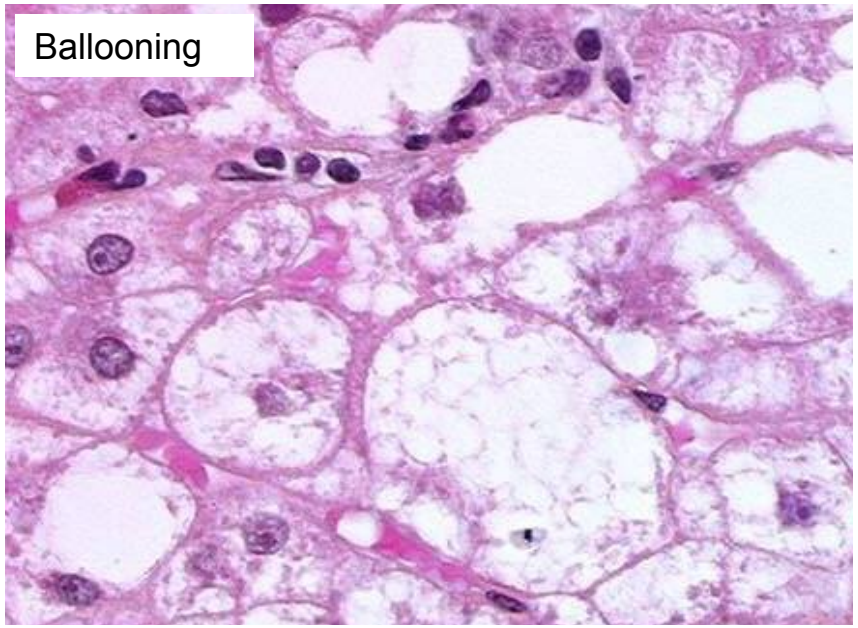


> 5% steatosis (≥ grade 1)
+ Lobular inflammation of any degree (≥ grade 1)
+ Liver cell ballooning of any amount (≥ grade 1)

"Endpoints and Clinical Trial Design for Nonalcoholic Steatohepatitis."
AJ. Sanyal, EM. Brunt, DE. Kleiner, KV. Kowdley, N. Chalasani, JE. Lavine, V. Ratziu, A.McCullough.
HEPATOLOGY 2011;54:344-353

• Activity (0-4) : Ballooning (0-2) + Lobular inflammation (0-2)





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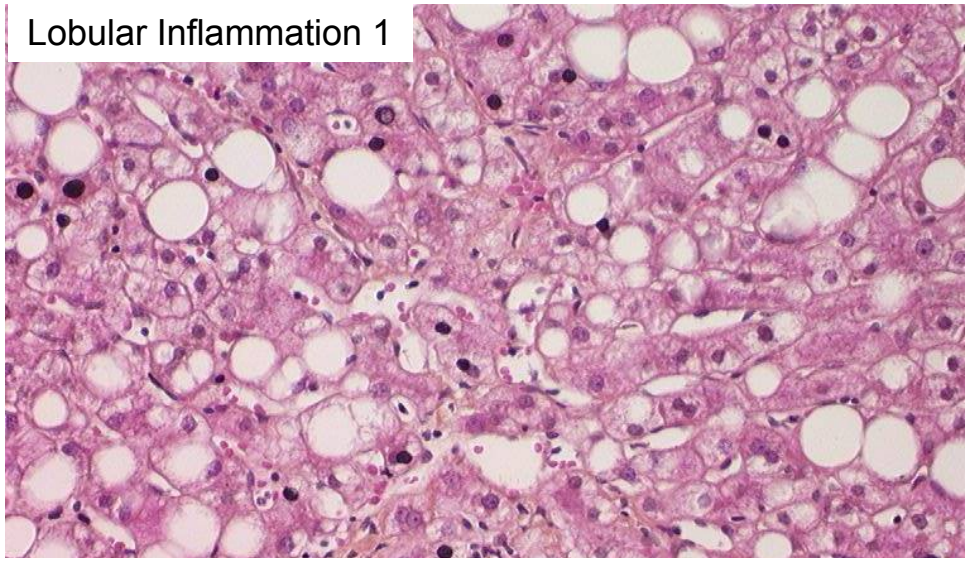
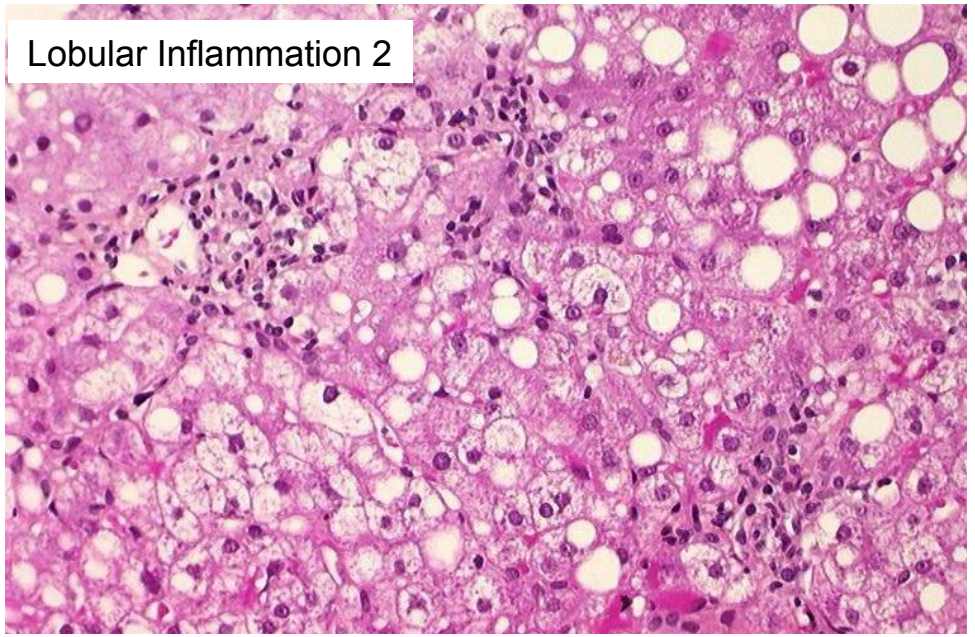
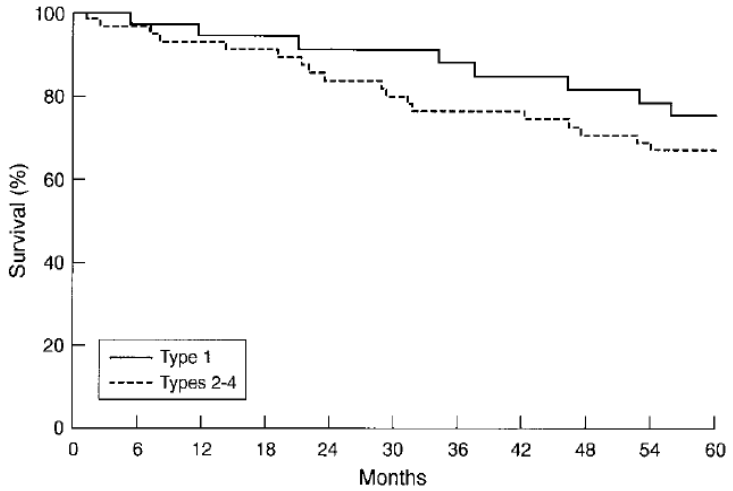




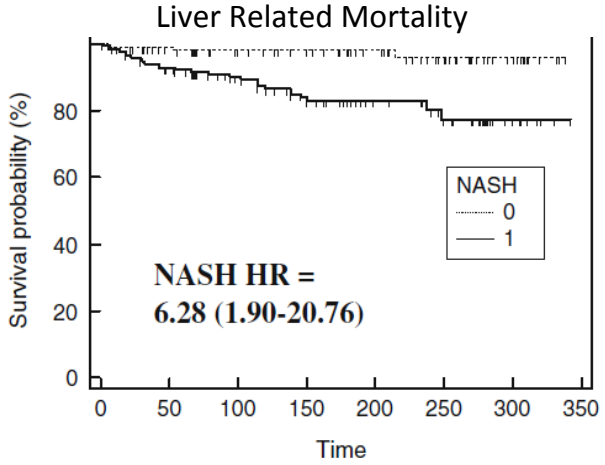
NASH : A histological disease clinically relevant

Overall survival in patients with steatosis and NASH



Matteoni CA, Younossi, Z, Gralich T et al. Gastro, 1999

Cumulative LRM according to presence of NASH
in index liver biopsy

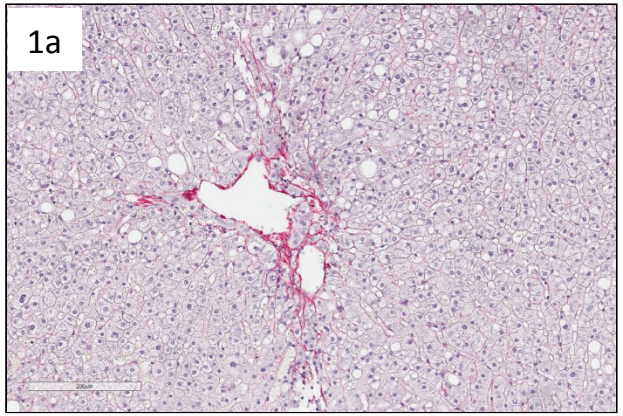


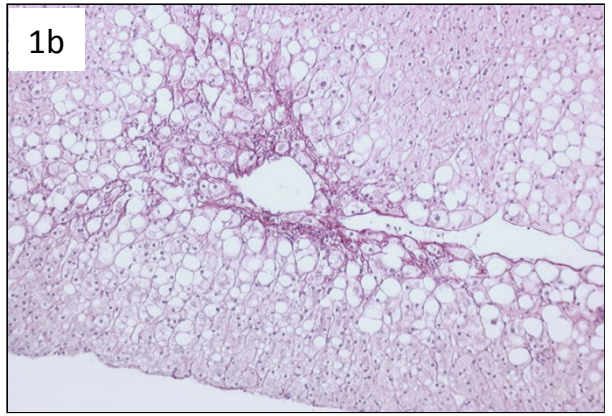
Stepanova M, Rafiq N, Makhlouf H et al. Dig Dis Sci 2013

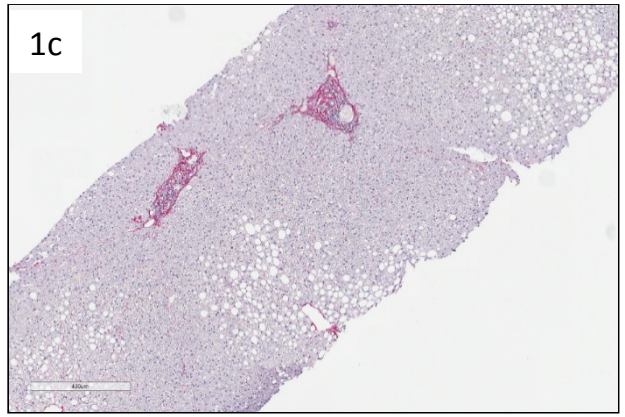
Patients with NASH have higher risk of liver mortality than steatosis

- **F**ibrosis (0 – 4) 1a,b,c = perisinusoidal or periportal fibrosis, 2 = both perisinusoidal and periportal fibrosis, 3 = bridging fibrosis, 4 = cirrhosis

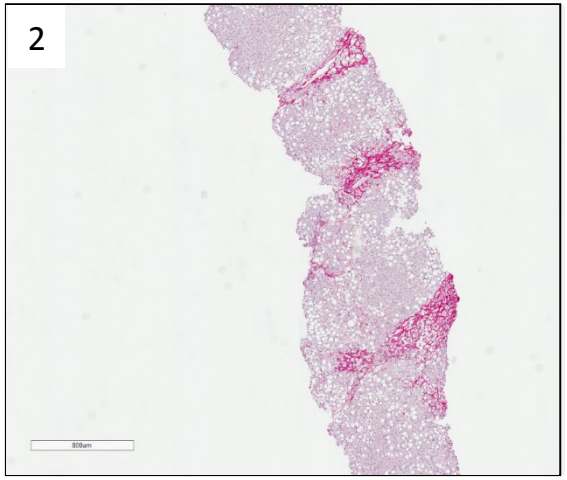
MILD FIBROSIS

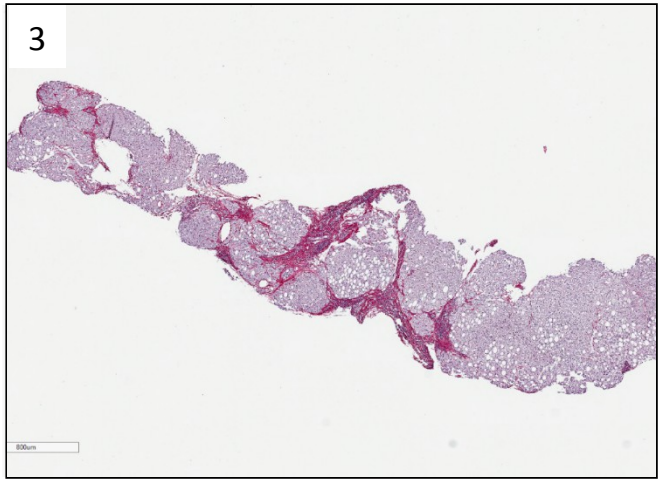


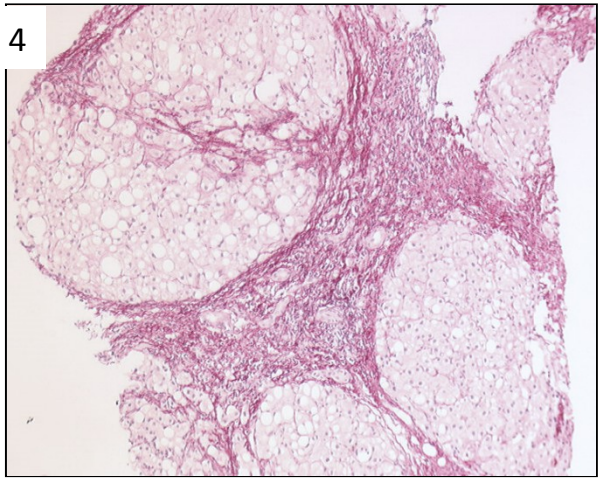




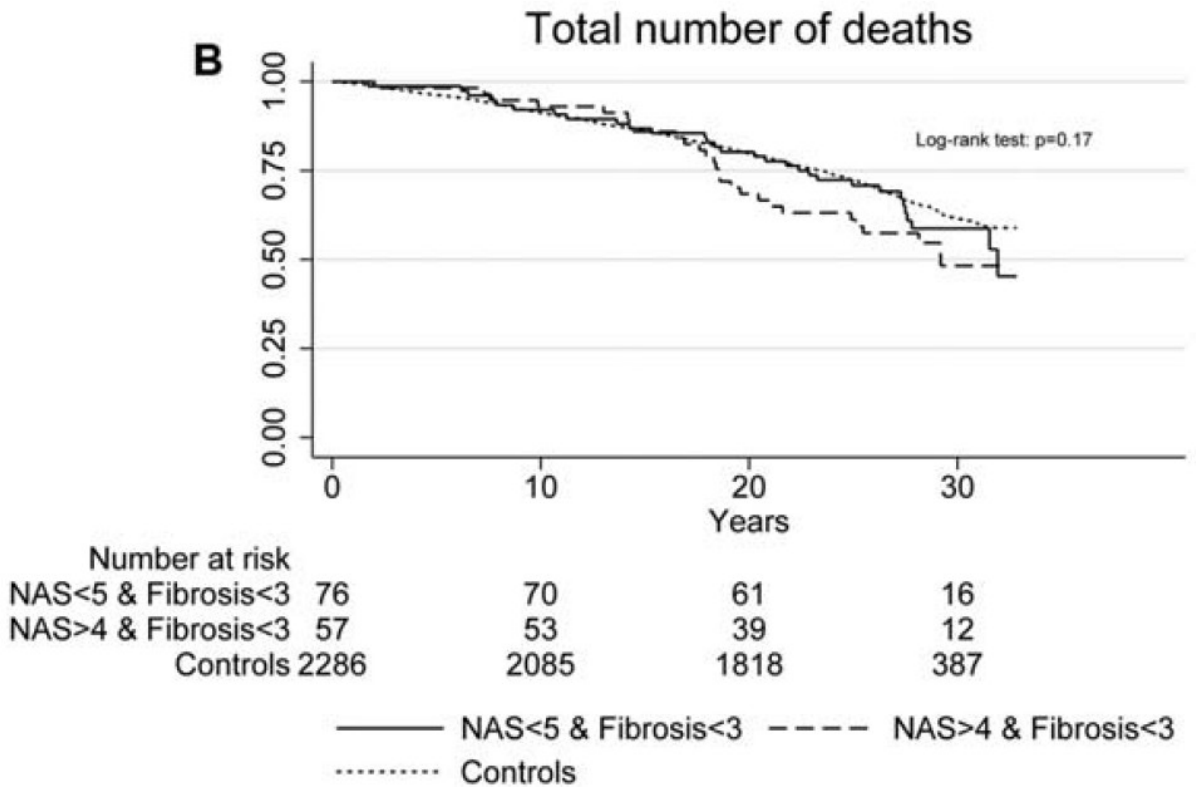
SIGNIFICANT FIBROSIS





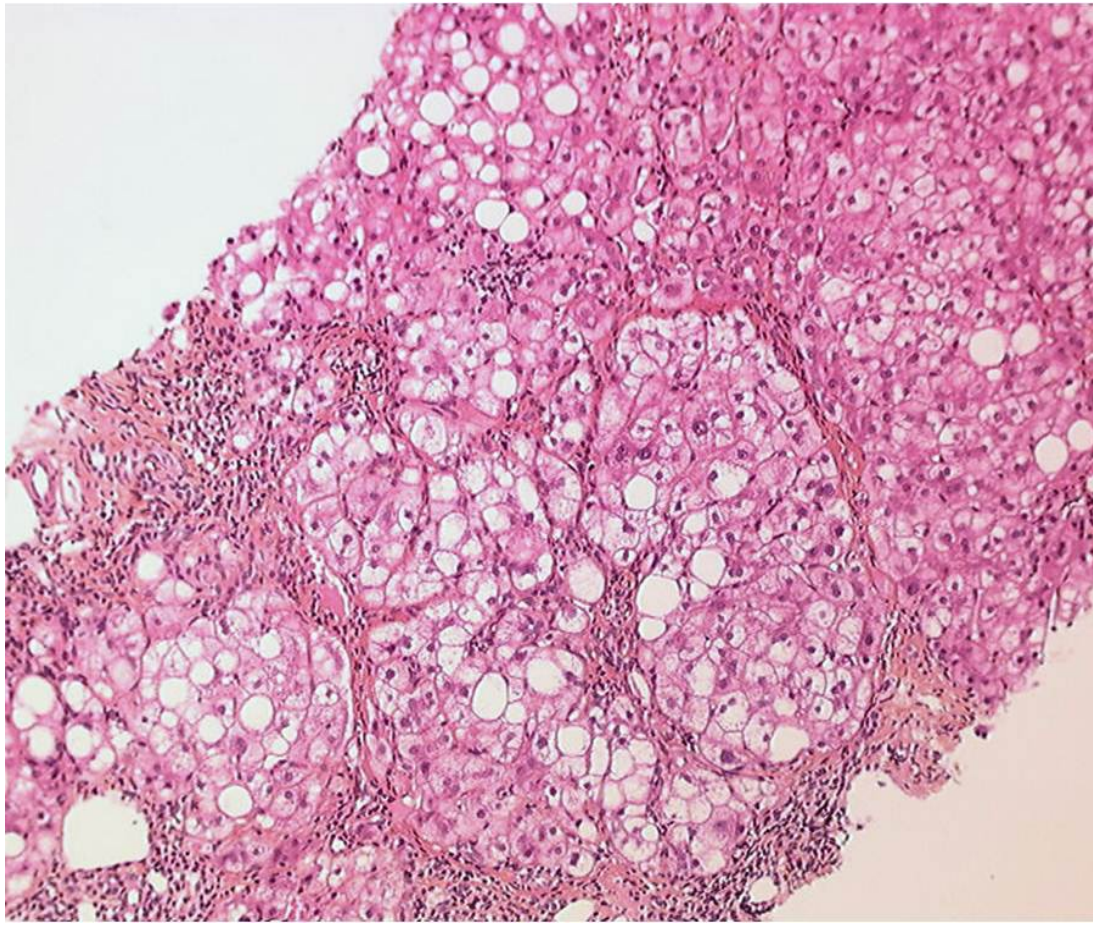


NASH (NAS > 5) have no deleterious evolution compared to a control population if fibrosis <3



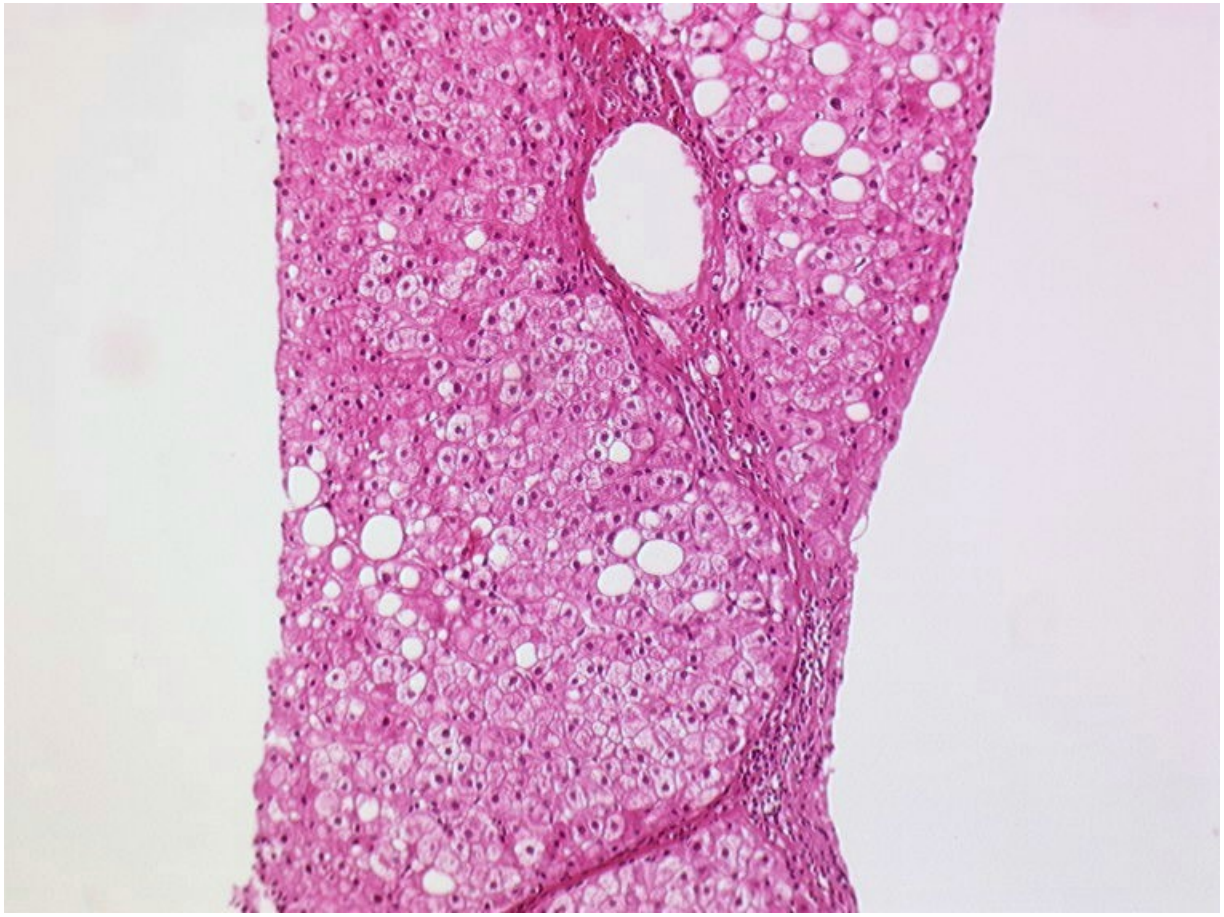
Ekstedt M, Hagström H, Nasr P et al, Hepatology 2015

S.A.F.



S2A4(2+2)F4

S.A.F.



S1A1F3

STEATOSIS : questions from the pathologist ?

- Accuracy of NI tools to evaluate amount of steatosis ?
- Do NI tools differentiate steatosis from NASH ?
- How to detect non invasively both NASH and fibrosis : does steatosis/NASH influence fibrosis accuracy detection with NI methods in NAFLD ?