

Is it still a place for liver biopsy in chronic viral hepatitis (C and B) ?

The opinion of a pathologist

Pierre Bedossa

Department of Pathology, Hôpital Beaujon,

University Paris-Denis Diderot

France

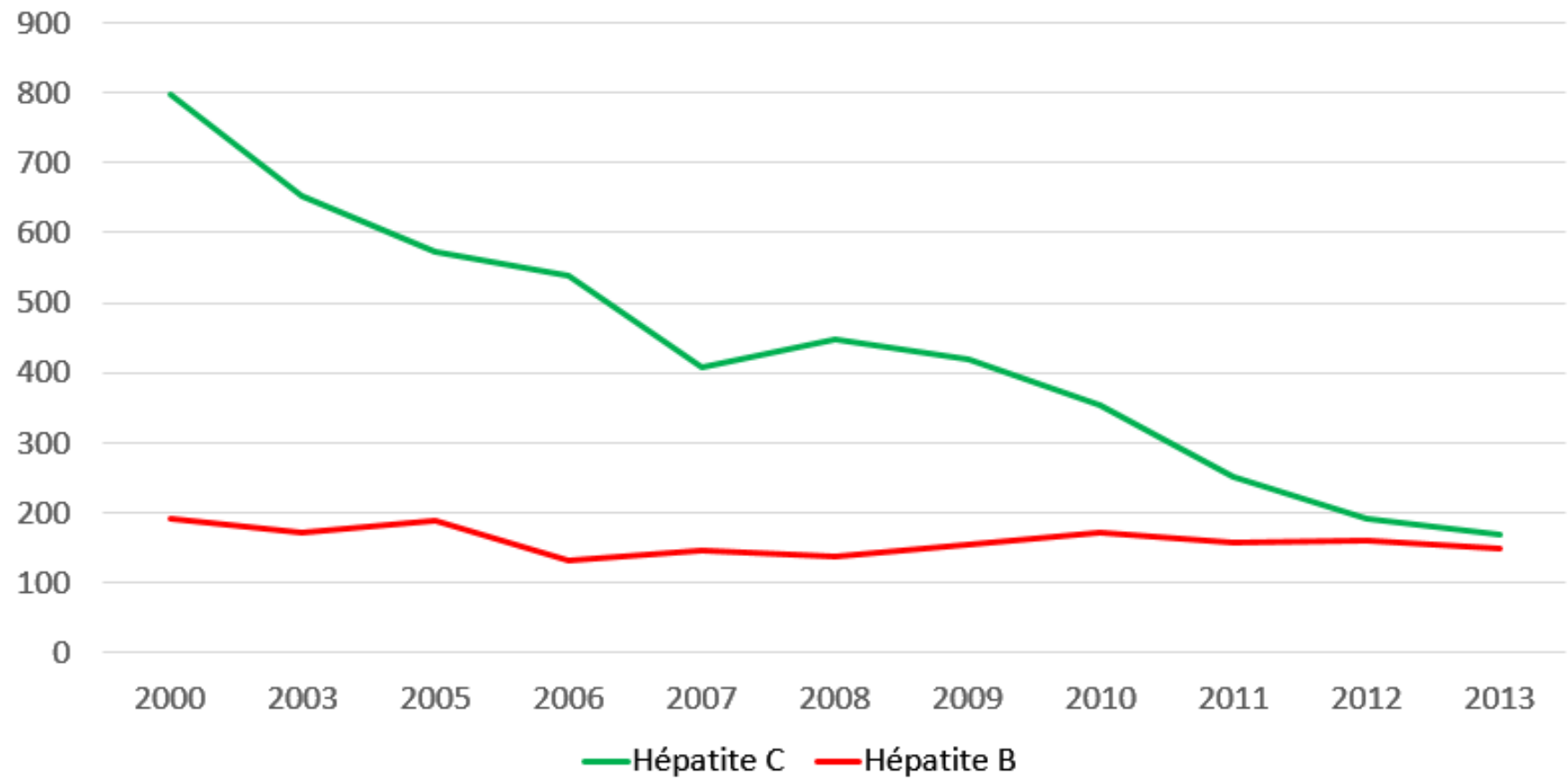


Inserm
U 773

UNIVERSITE
PARIS7-DENIS DIDEROT
UMRS 773



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



Issues to be discussed

- Is there remaining indications of liver biopsy in hepatitis C ?
- Liver biopsy in hepatitis B
- Liver biopsy in the context of fibrosis regression after antiviral treatment

Is there remaining indications of liver biopsy in hepatitis C ?

Decline in the indications of liver biopsy in Hep C

➤ Major progress of antiviral treatment in Hep C :

- Highly efficient
- Wide indications
- short duration
- Adverse events well-characterized

➤ Liver biopsy is no more useful :

clinical issues : cirrhosis vs non cirrhosis ?, normal liver vs any fibrosis ?

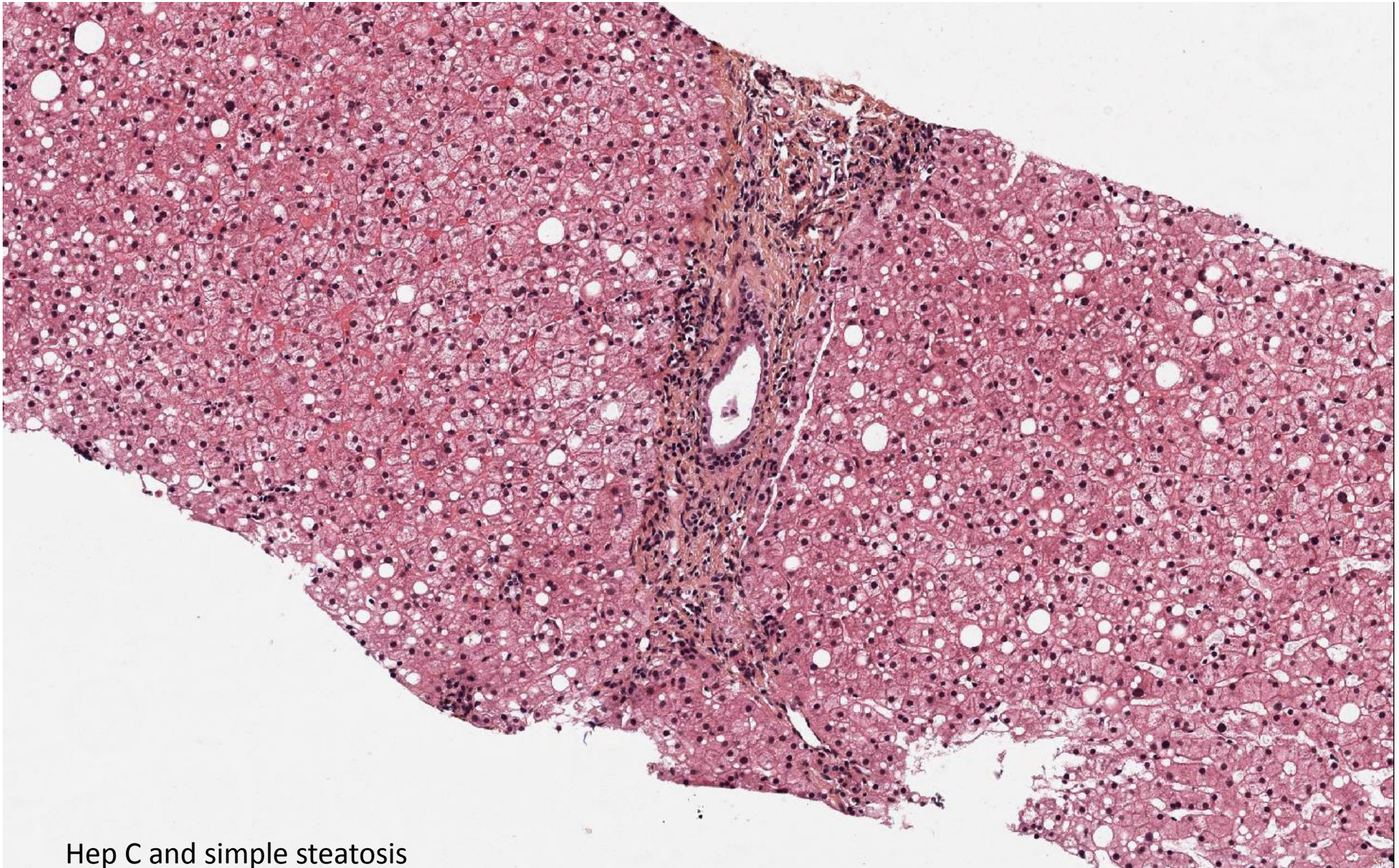
→ non invasive markers (serum, Fibroscan)

Is there remaining indications of liver biopsy in hepatitis C ?

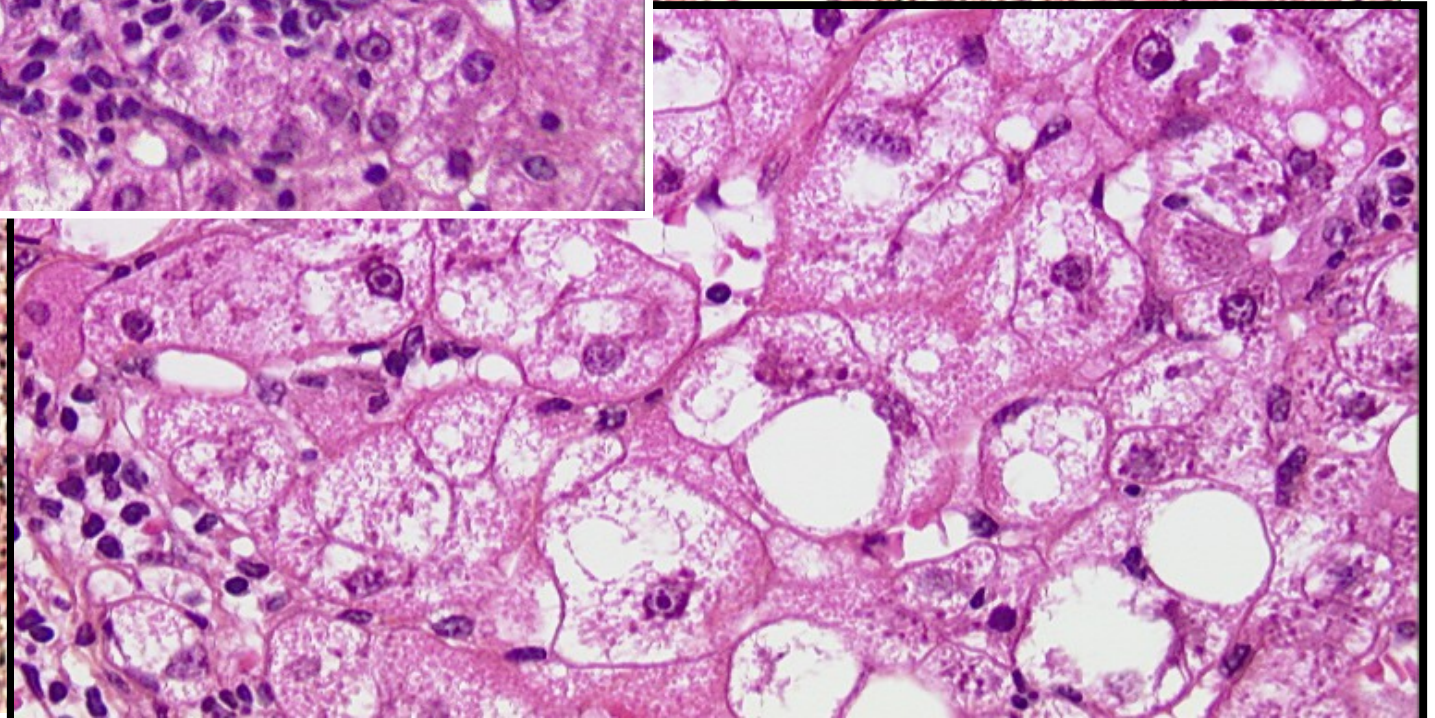
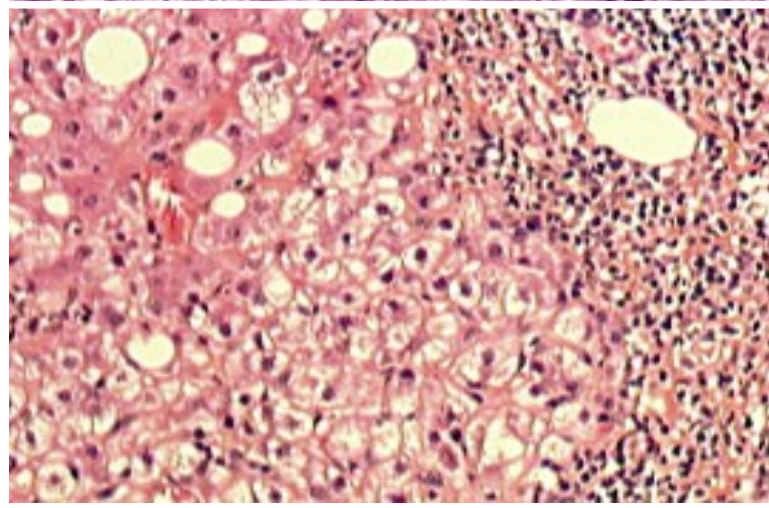
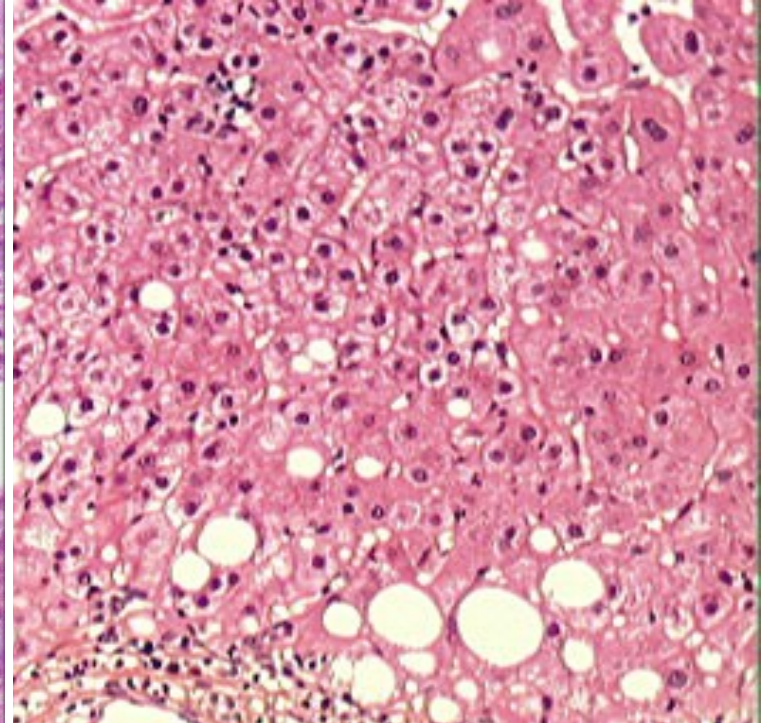
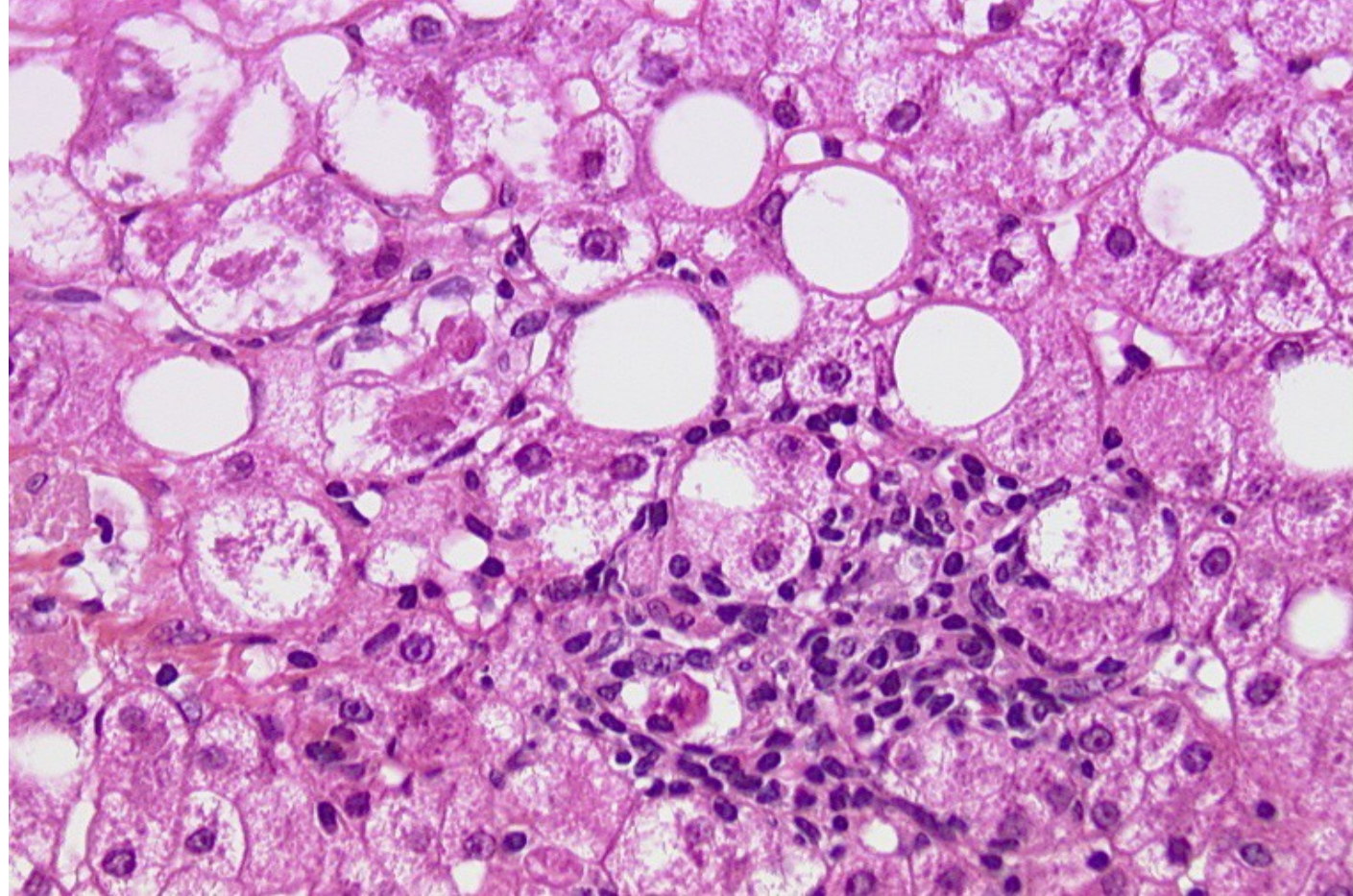
When to perform still a liver biopsy in hepatitis C :

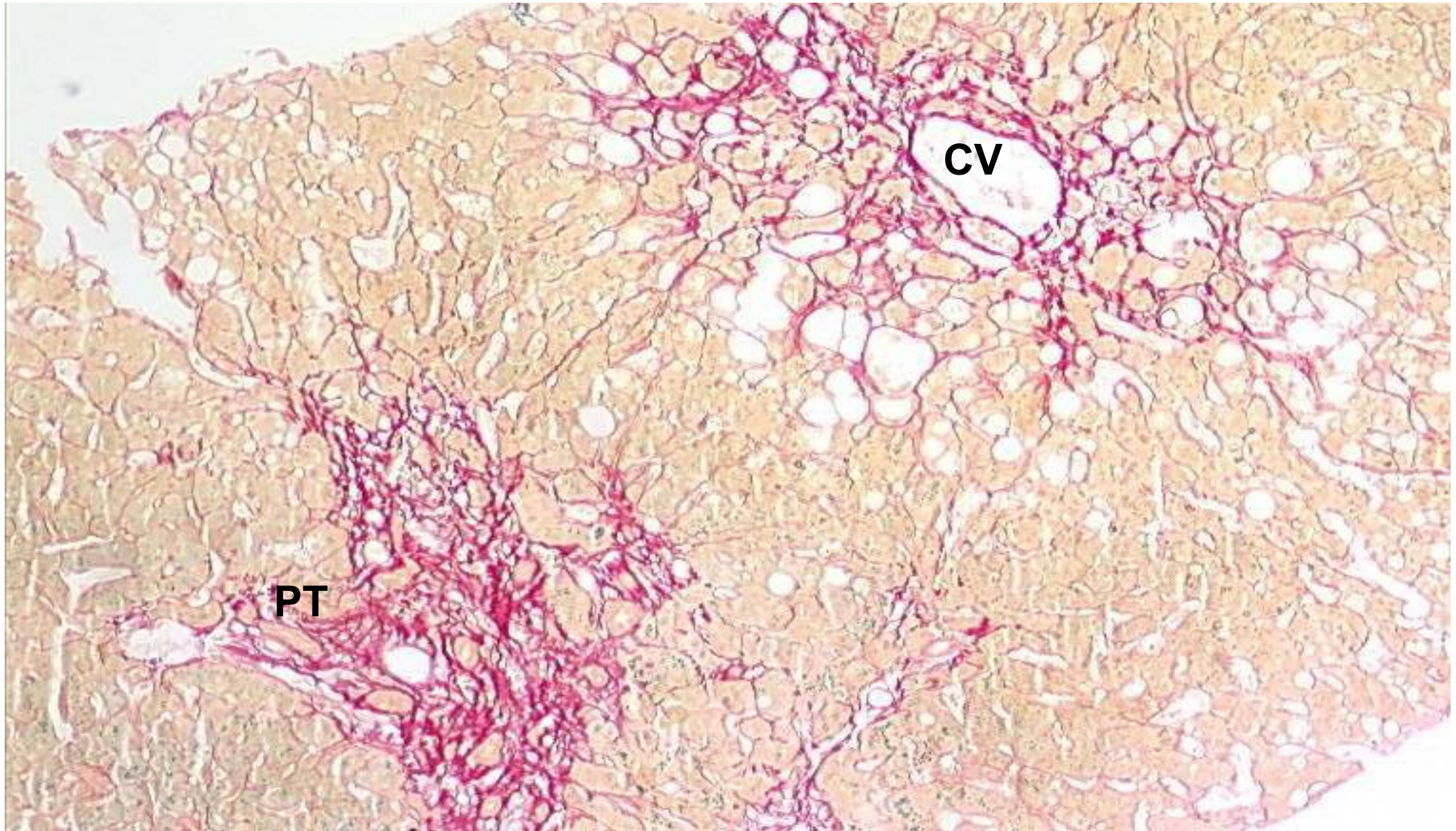
- Evidence of comorbidities

NAFLD and HEP C



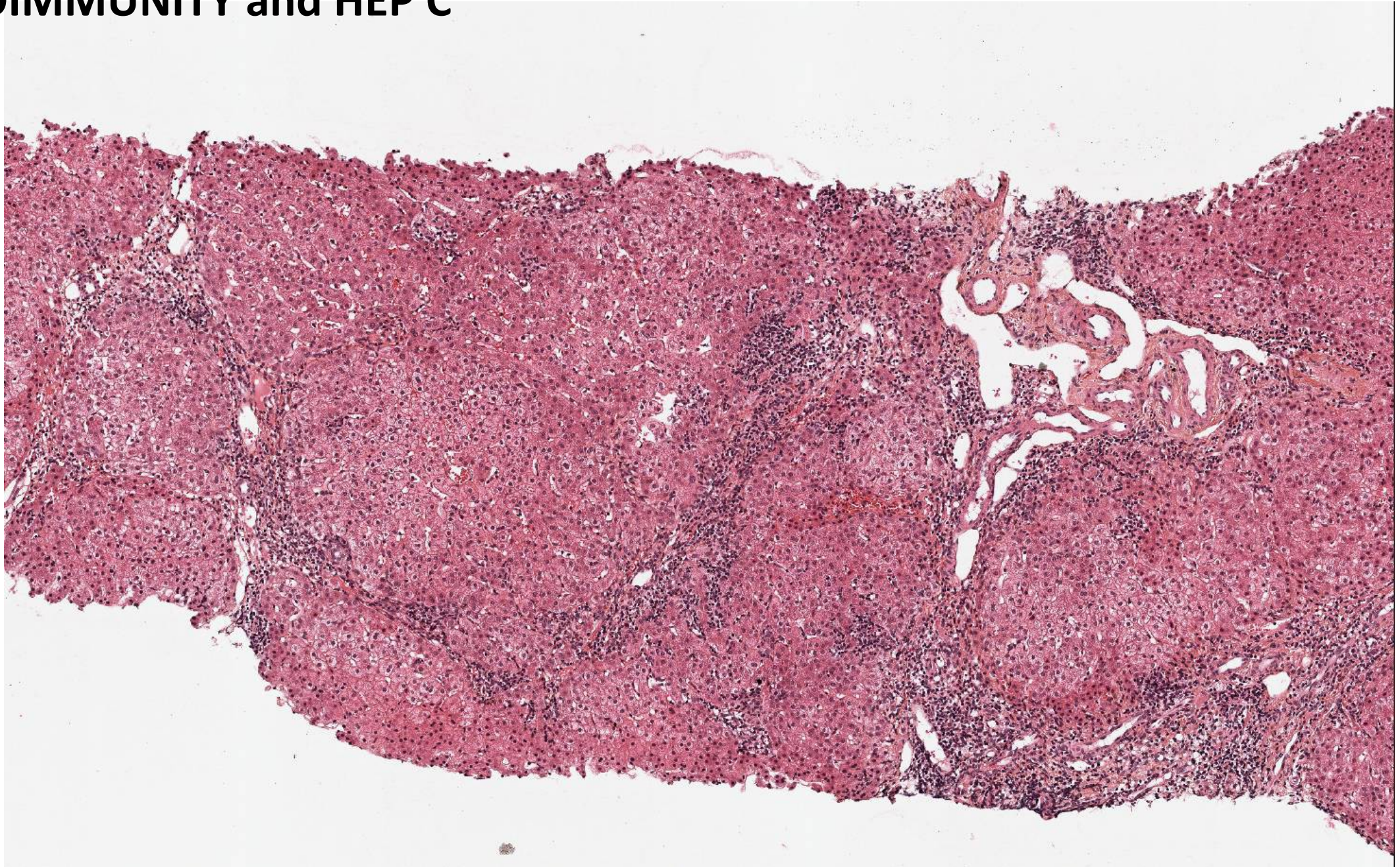
Hep C and simple steatosis

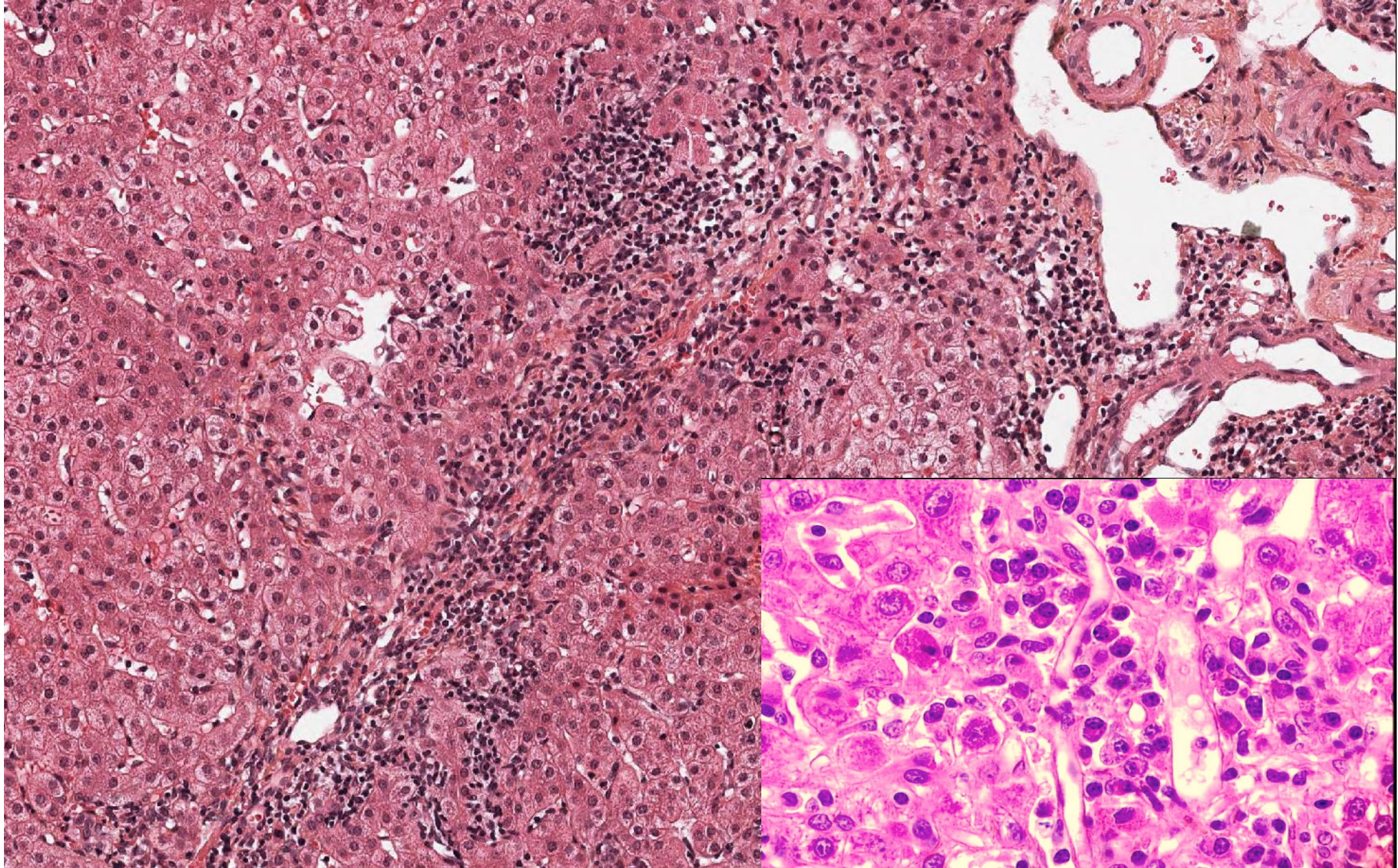




Hep C + NASH : portal fibrosis (HepC) + central fibrosis (NASH)

AUTOIMMUNITY and HEP C





Is there remaining indications of liver biopsy in hepatitis C ?

When to perform still a liver biopsy in hepatitis C :

- Evidence of comorbidities
 - Others: drug interaction, iron, granulomas..... and unexpected associated diseases
- Discordances between non invasive markers (serum vs Fibroscan) or non invasive markers and symptoms
- Patients difficult to treat, retreatment, any complex situation
- Follow-up of transplanted patients for cirrhosis C

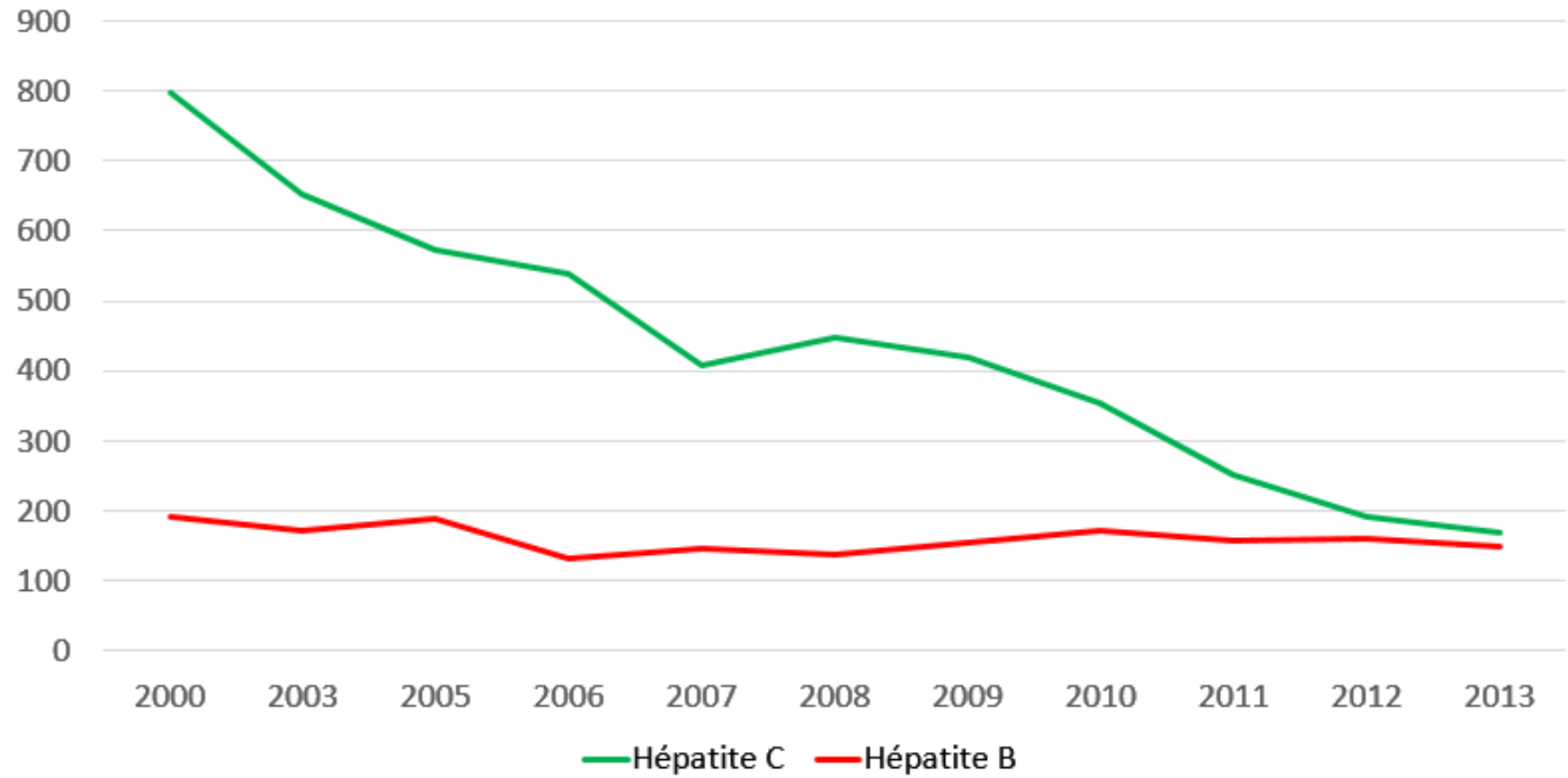
Remaining indication of liver biopsy in Hep C : 10 – 20% of Hep C patients in tertiary care hospital

Is there remaining indications of liver biopsy in hepatitis C ?

Comments ?

Questions ?

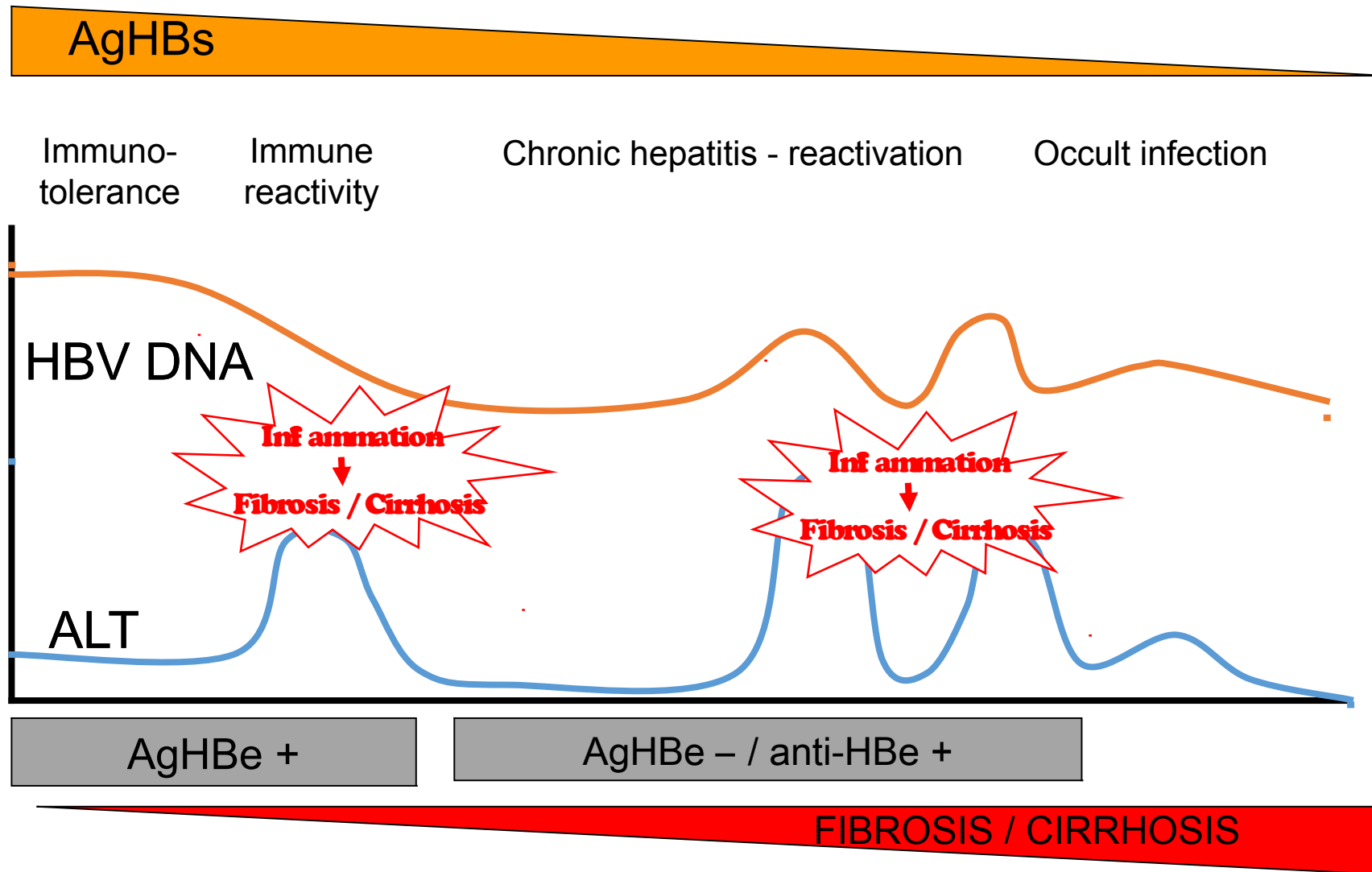
Number of liver biopsy per year from 2000 to 2013 for chronic viral hepatitis in Beaujon hospital



Liver biopsy in hepatitis B

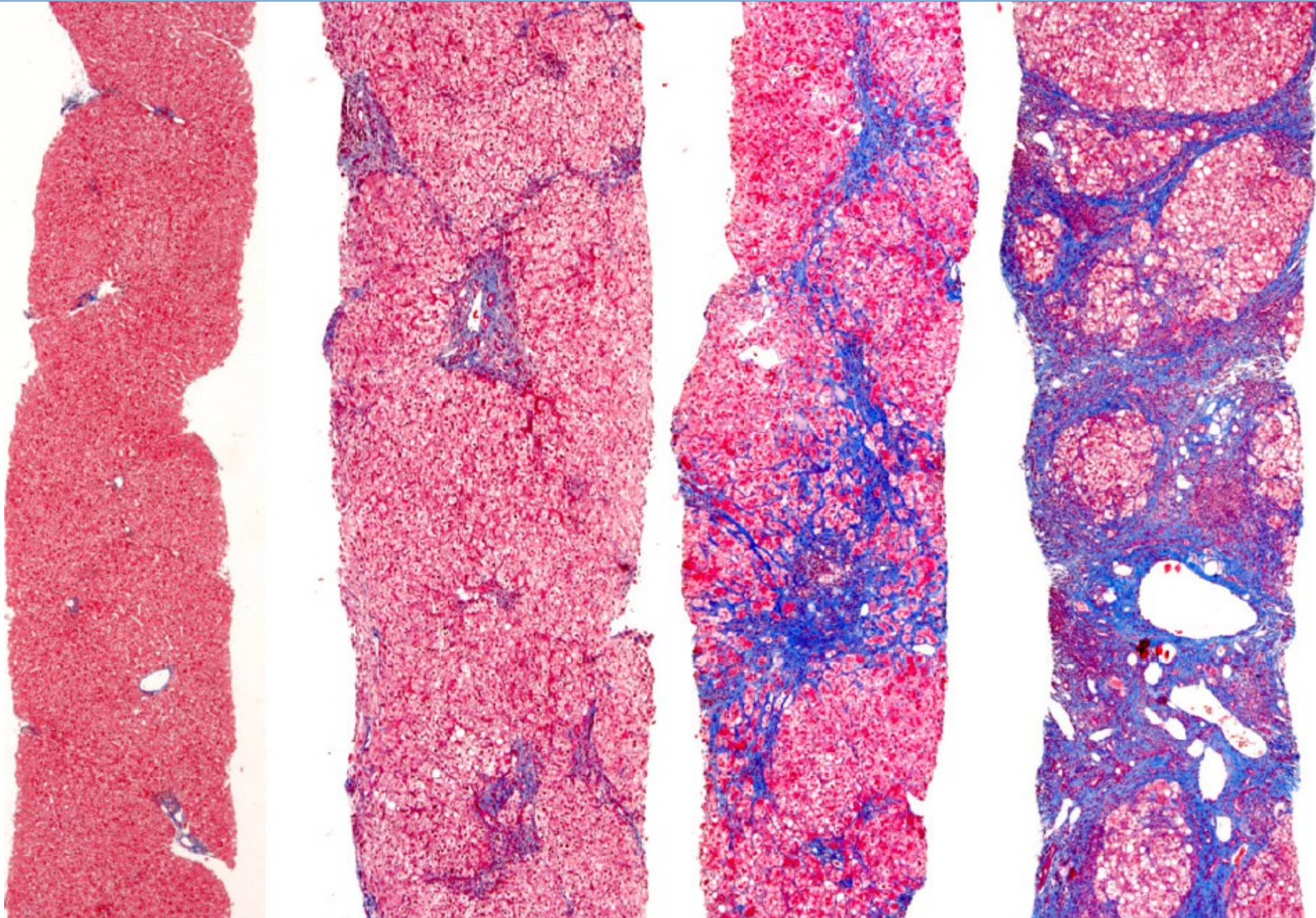
- Different context than Hep C :
 - Viral Suppression not eradication
 - Long-term treatment
 - Cost, observance
 - Adverse events after long-time use ?
- **Helpful to decide the best timing for starting treatment : not too early – not too late (in addition to viral makers and transaminases)**

Hepatitis B : natural history is more complex



Neither HBV DNA quantification, HBs Ag, transaminases or HBeAg allow, alone or in combination, to assess histological severity (grade and stage)

Liver biopsy should be considered in pre-treatment evaluation of HEP B (EASL guidelines 2012)



Liver biopsy in Hepatitis B

- CON :

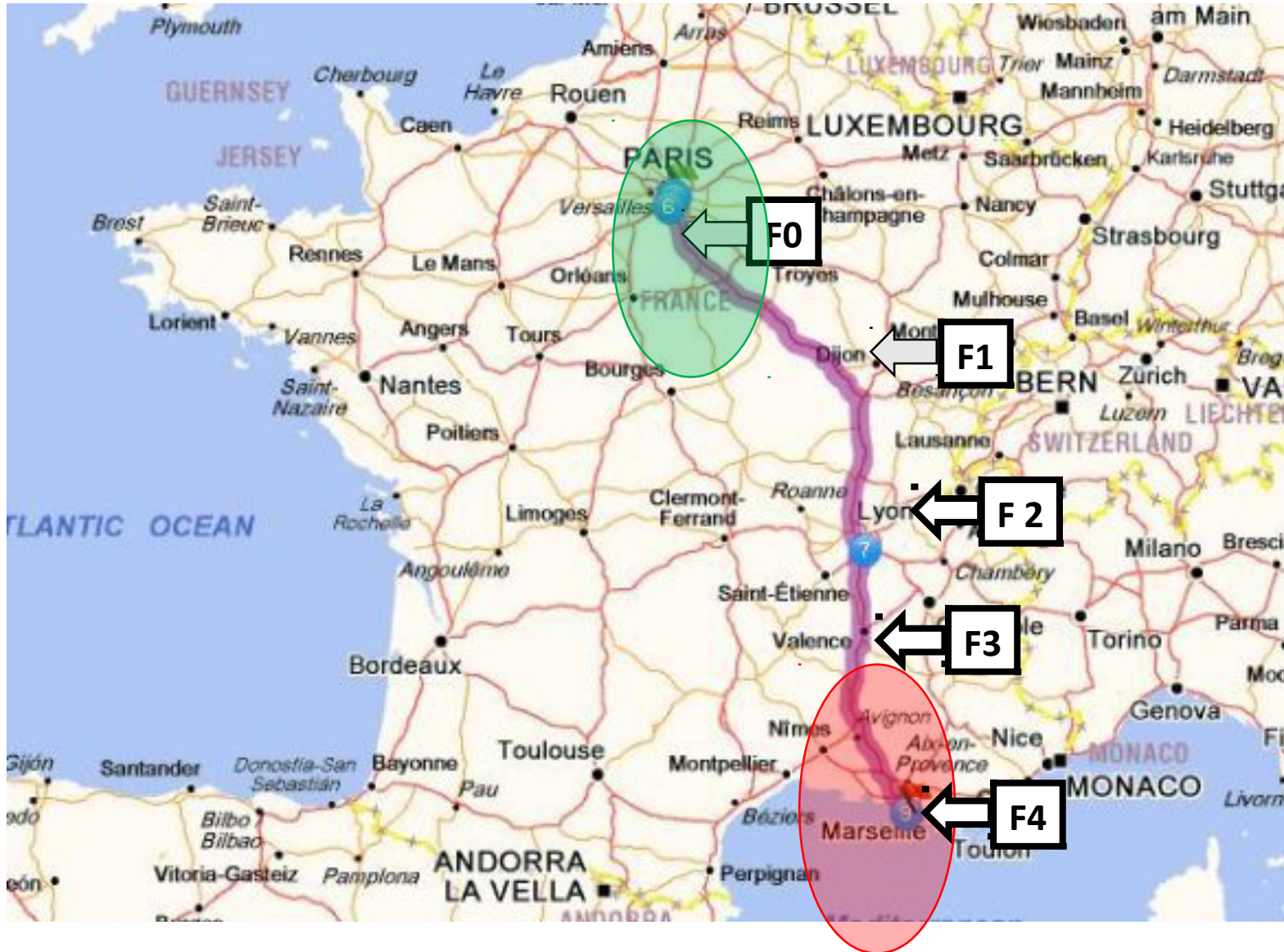
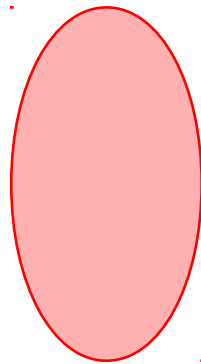
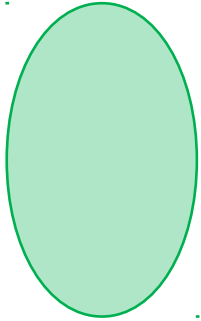
- Invasive
- Acceptability
- Accessibility
- Cost
- Sampling error

- PRO

- Gold Standard
- Fibrosisbut not only
- NI markers risk of errors:
 - LB is the reference for serum marker :
LB error impact accuracy of NI markers
 - Histological confounding patterns

From Paris (F0) to Marseille (F4)

Non invasive
markers



Liver biopsy

F0

F1

F2

F3

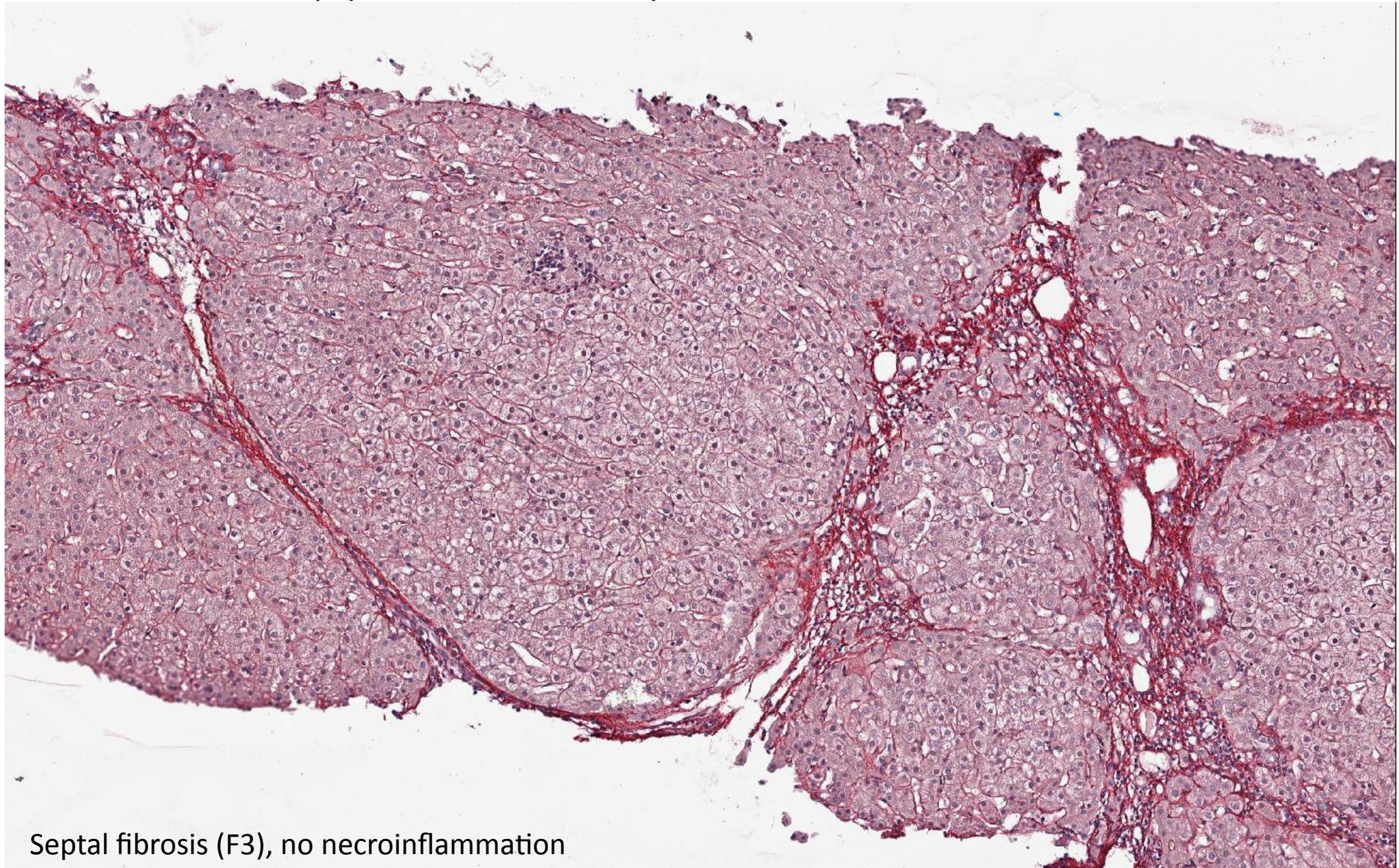
F4

From Paris (F0) to Marseille (F4)



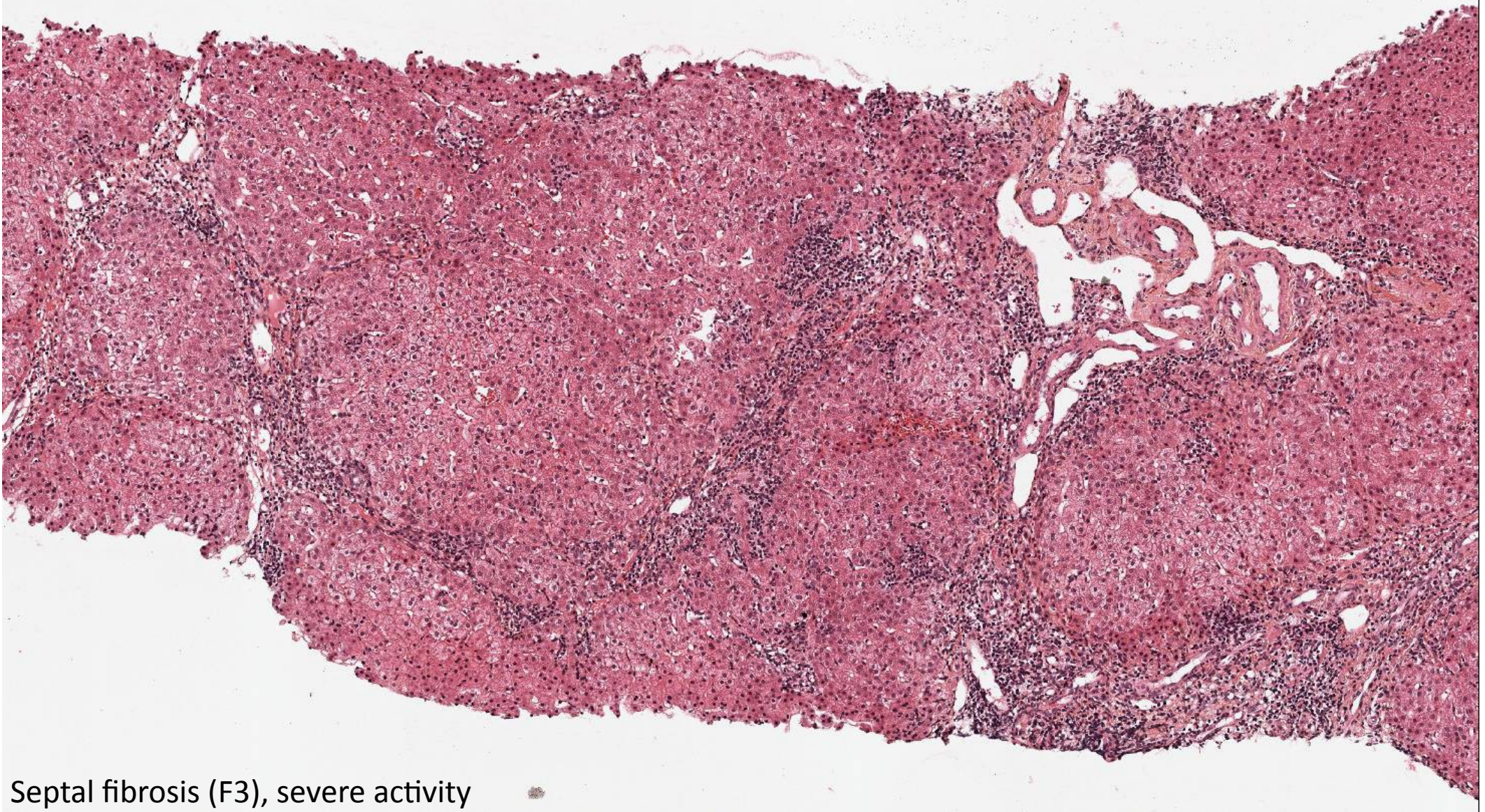
- Non invasive markers: static evaluation of fibrosis
 - Liver biopsy: dynamic evaluation of fibrosis

Liver biopsy: fibrosis but not only..... Fibrosis in its microenvironment



Septal fibrosis (F3), no necroinflammation

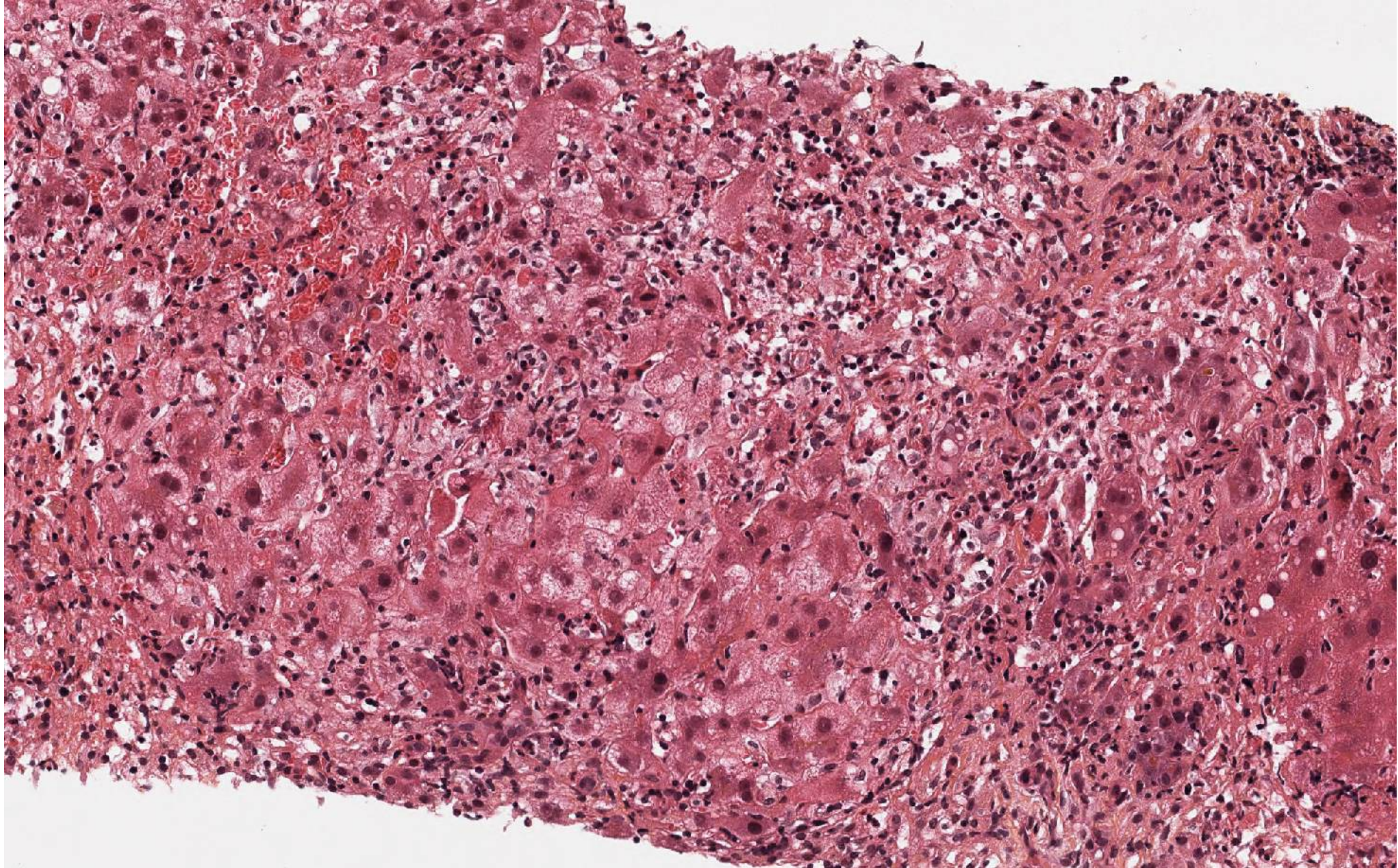
Liver biopsy: fibrosis in its microenvironment



Septal fibrosis (F3), severe activity

Hepatitis B, necroinflammation and fibrosis evaluation

- Inflammation : a characteristic histological pattern in Hepatitis B
- Necroinflammation : confounding factor in fibrosis evaluation with non-invasive marker (serum markers and Fibroscan) in the context of Hep B



Viral reactivation : Fibroscan = 25 Kpa, Fibrosis F2

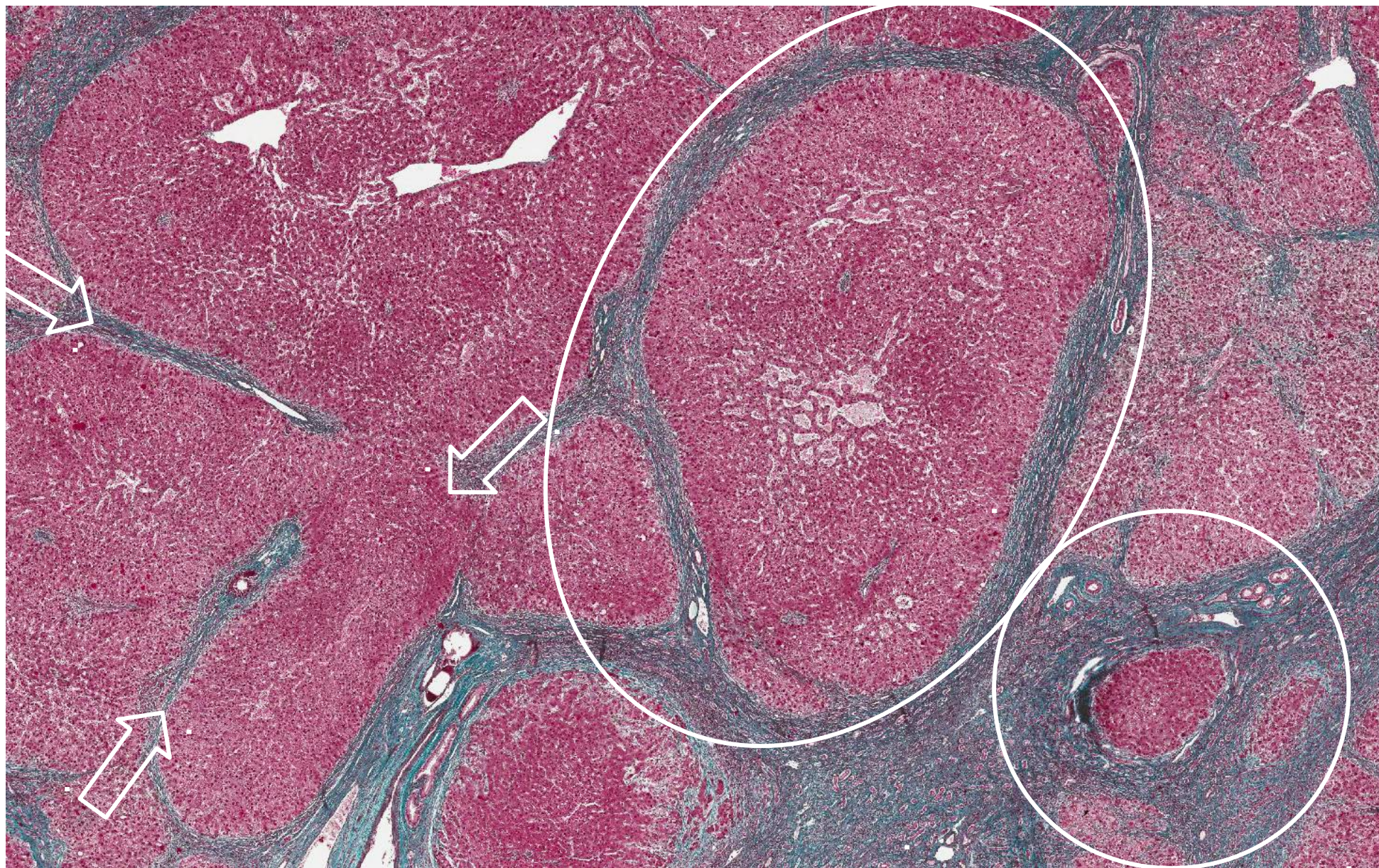
Liver biopsy has still a significant role in hepatitis B

Comments ?

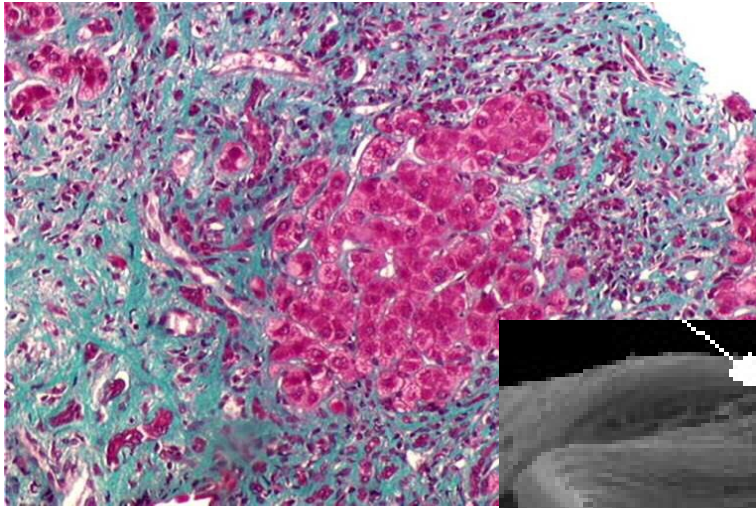
Questions ?

Issues to discuss

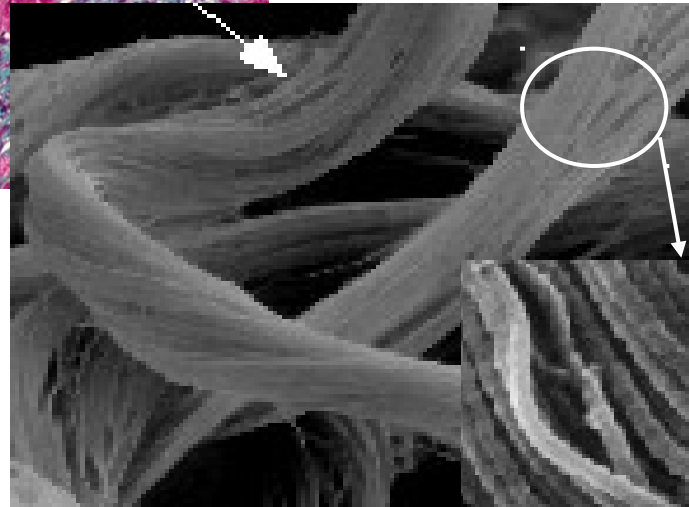
- Is there remaining indications of liver biopsy in hepatitis C ?
- Liver biopsy in Hepatitis B
- ✓ Liver biopsy in the context of fibrosis regression after antiviral treatment (Hep B, Hep C)



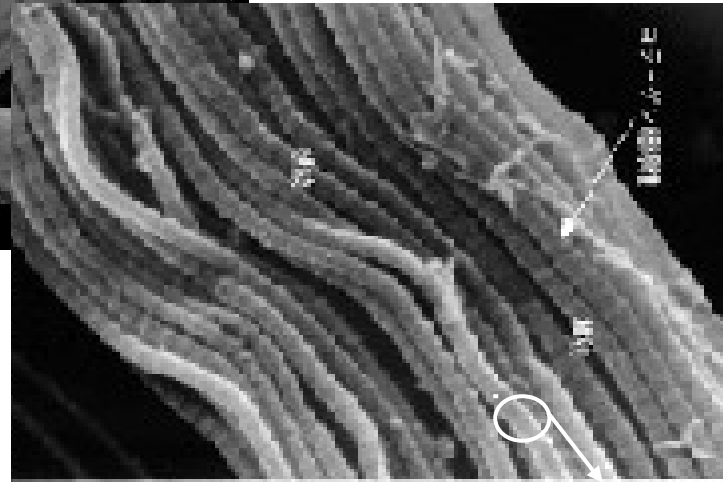
Fibrosis : complex, resistant and stable architecture



Fibrous septa



Fibres

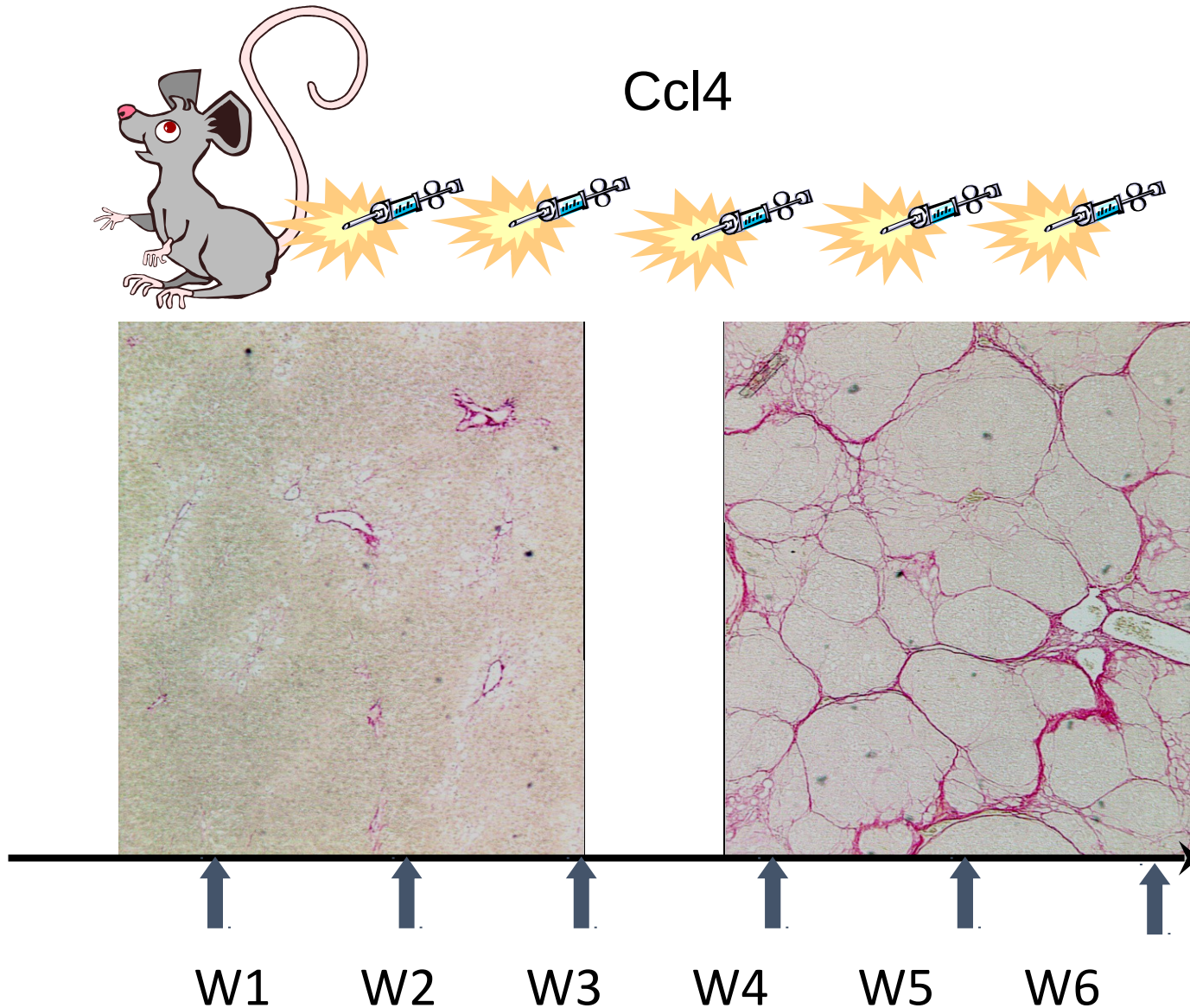


Fibrills



Cirrhosis of the liver: a reversible disease ?

Perez-Tamayo R. Pathol Annu 1979;14:183-213



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'Hépatogastroentérologie, 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'Hépatogastroentérologie, 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

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 ratio [OR] = 0.12; $P < 0.0001$), sustained viral response (OR = 0.36; $P < 0.0001$), age < 40 years (OR = 0.51; $P < 0.001$), body mass index < 27 kg/m² (OR = 0.65; $P < 0.001$), no or minimal baseline activity (OR = 0.70; $P = 0.02$), and viral load < 3.5 millions copies per milliliter (OR = 0.79; $P = 0.03$). **Conclusions:** PEG-interferon and ribavirin combination significantly reduces the rate of fibrosis progression in patients with hepatitis C.

Approximately 170 million people worldwide are infected with chronic hepatitis C virus (HCV).¹ The degree of histologic fibrosis is an important marker of the stage of the disease² because the natural history of hep-

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 monotherapy⁸⁻¹⁰ or in combination with ribavirin.¹¹ The effect of these new regimens on histo-

logical changes on the m... risk fact... taken to determine the impact of therapy in patients who eradicate the virus, and also in patients who do not eradicate the virus during therapy.

Materials and Methods

The individual data from 4 randomized trials of PEG-interferon alfa-2b alone (Pegintron, Schering Plough, Kenilworth, NJ),⁸ or in combination with ribavirin,¹¹ or of the combination

Abbreviations used in this paper: PEG, pegylated; TIW, three times per week.

© 2002 by the American Gastroenterological Association
0016-5085/02/\$35.00
doi:10.1053/gast.2002.33023

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

Evolution histologique de la fibrose dans l'hépatite B après suppression virale

- **Lamivudine** : 63 patients, regression de la fibrose septale chez 12/19 (63%) et de la cirrhose chez 8/11 patients **(73%)**

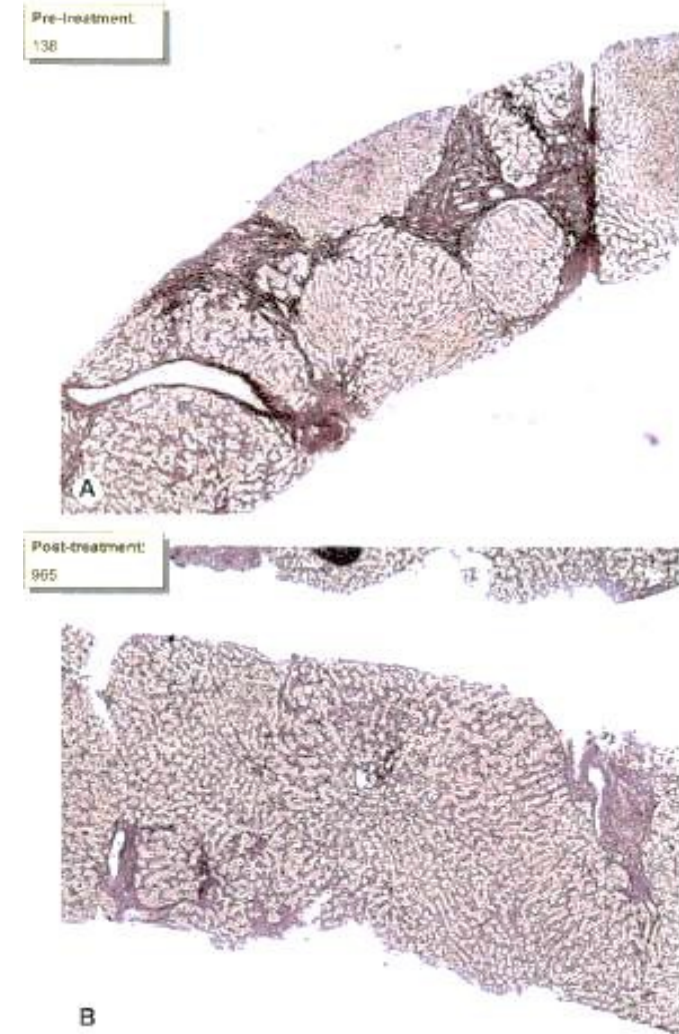
Dienstag JL, et al. *Gastroenterology* 2003; **124**:105–117

- **Adefovir** : Régression de F3 / F4 chez 7/12 patients **(58%)**

Hadziyannis G, et al. *Gastroenterology* 2006; **131**:1743–1751

- **Entecavir** : **88%** des patients réduisait leur score de fibrose dont tous les patients avec fibrose septale ou cirrhose au départ

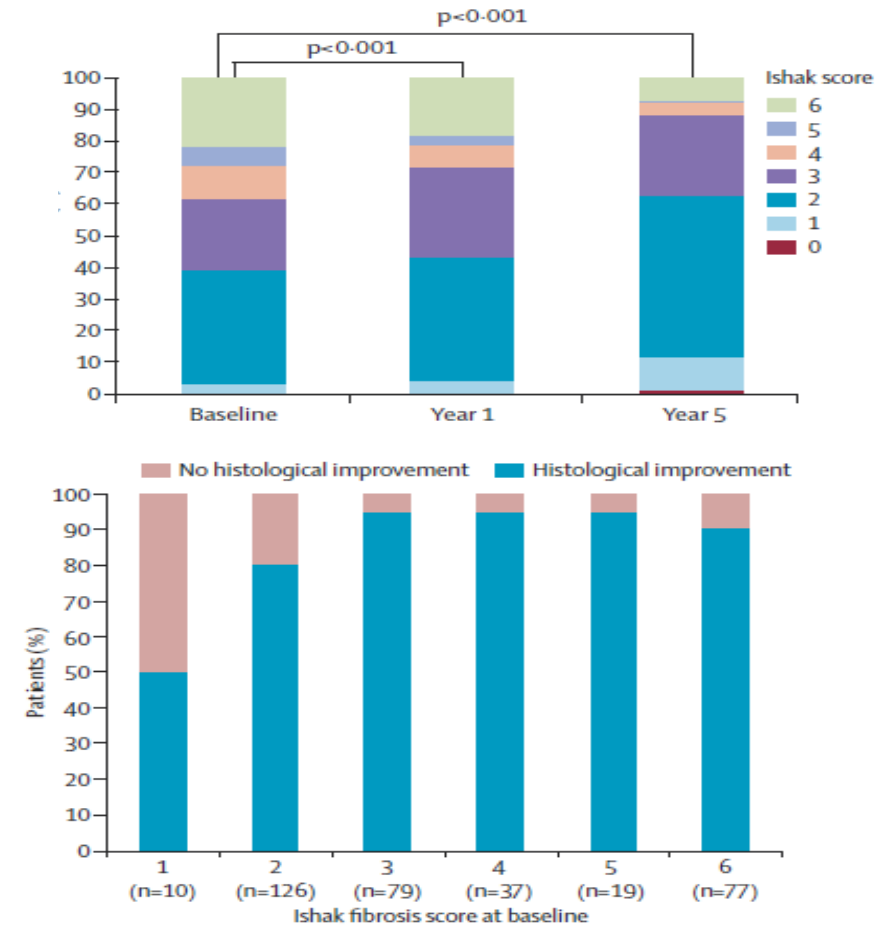
Chang TT, et al. *Hepatology* 2010; **52**:886-93



Histological outcome in Hep B after long-term tenofovir treatment

- 348 patients with paired biopsies before and after 5 years treatment with tenofovir DF
- 51% (176/348) of patients had fibrosis regression (≥ 1 unit \searrow in Ishak score) and 96% had prevention of fibrosis progression
- Cirrhosis (Ishak ≥ 5) regression occurred in 71/96 of patients (74%) with cirrhosis at baseline

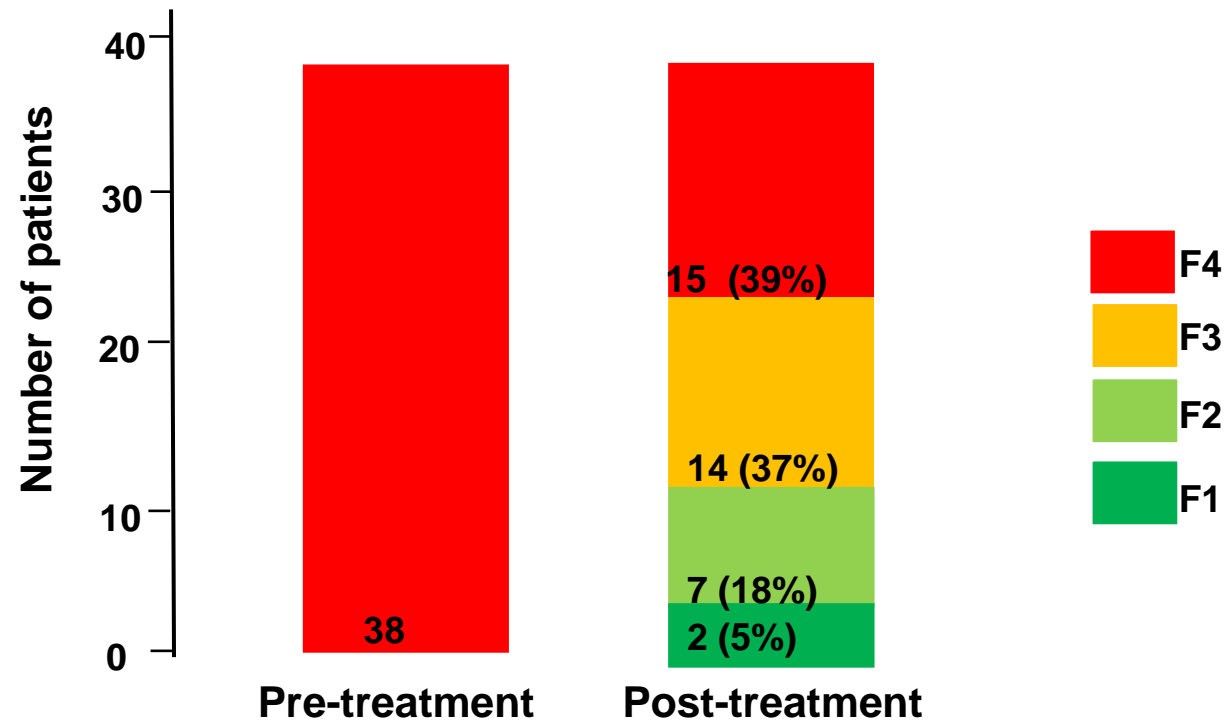
Long-term suppression of HBV can lead to regression of fibrosis and cirrhosis



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

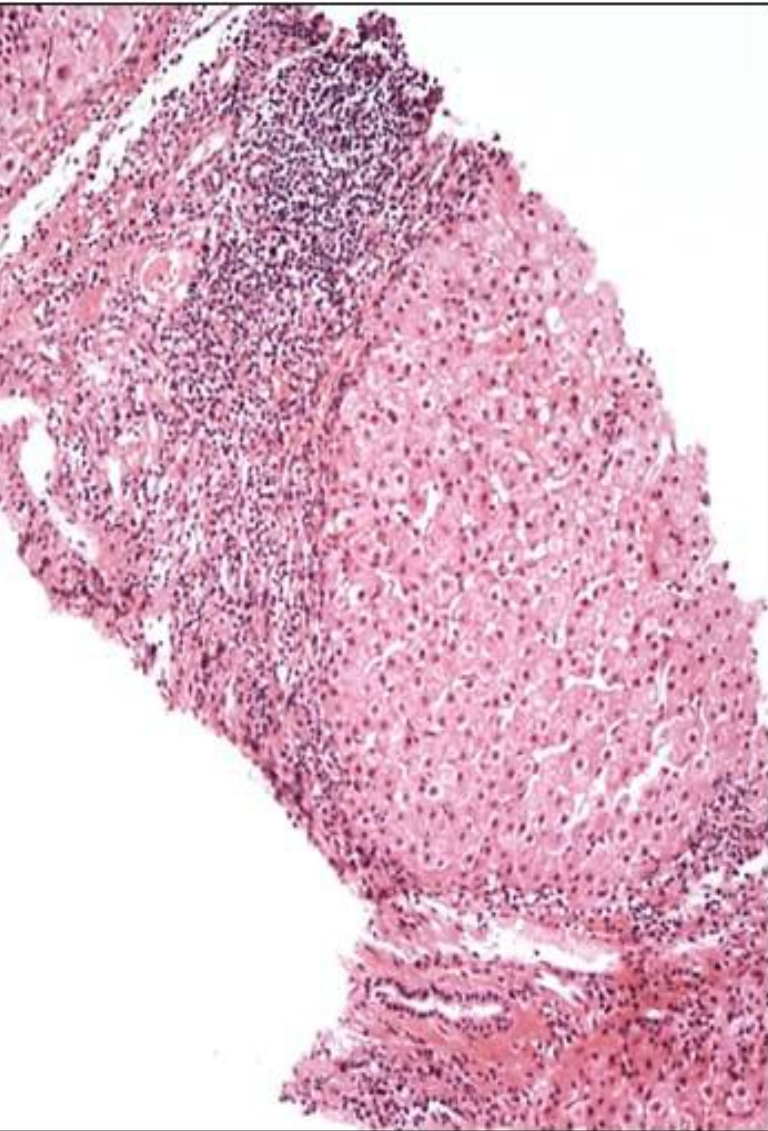
D'Ambrosio *et al* *Hepatology*. 2012

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

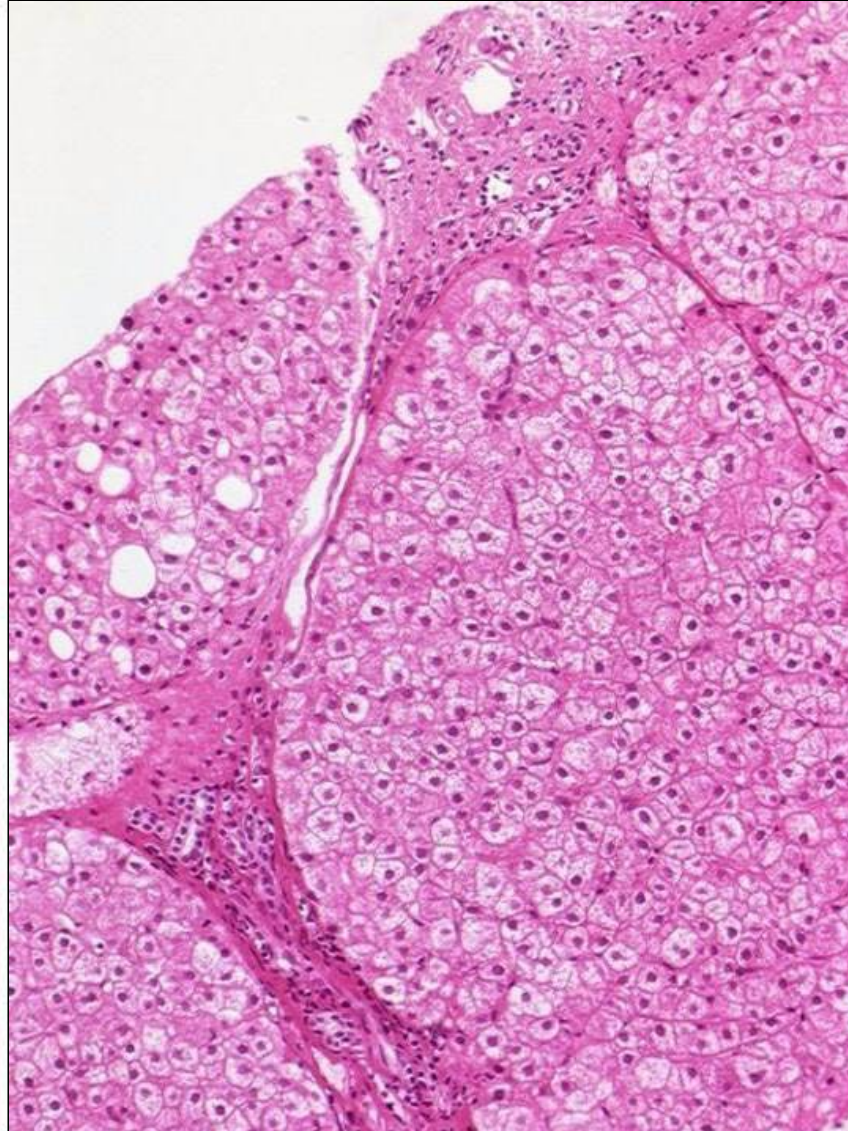


61% patients with F4 at baseline had cirrhosis regression to lower METAVIR stages

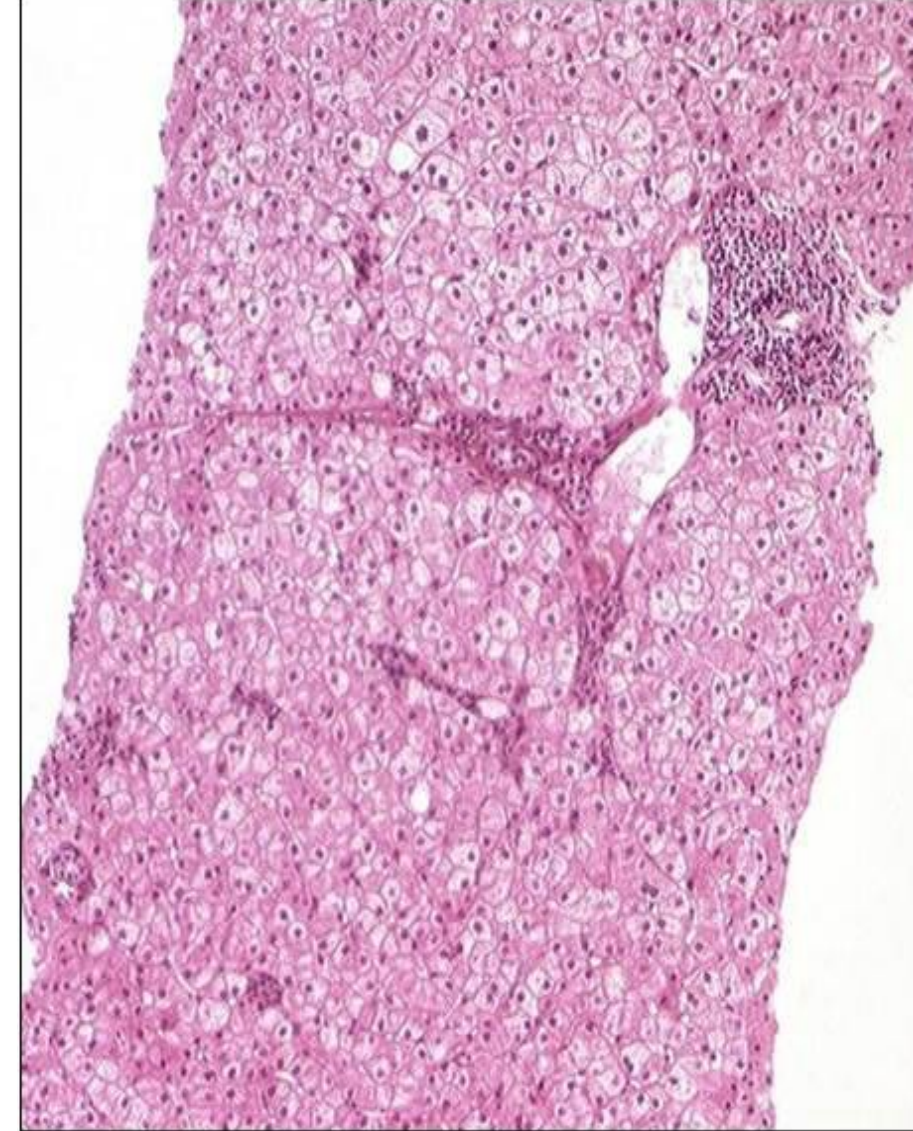
CIRRHOSIS C
PRETREATMENT BIOPSY



1 year AFTER SVR

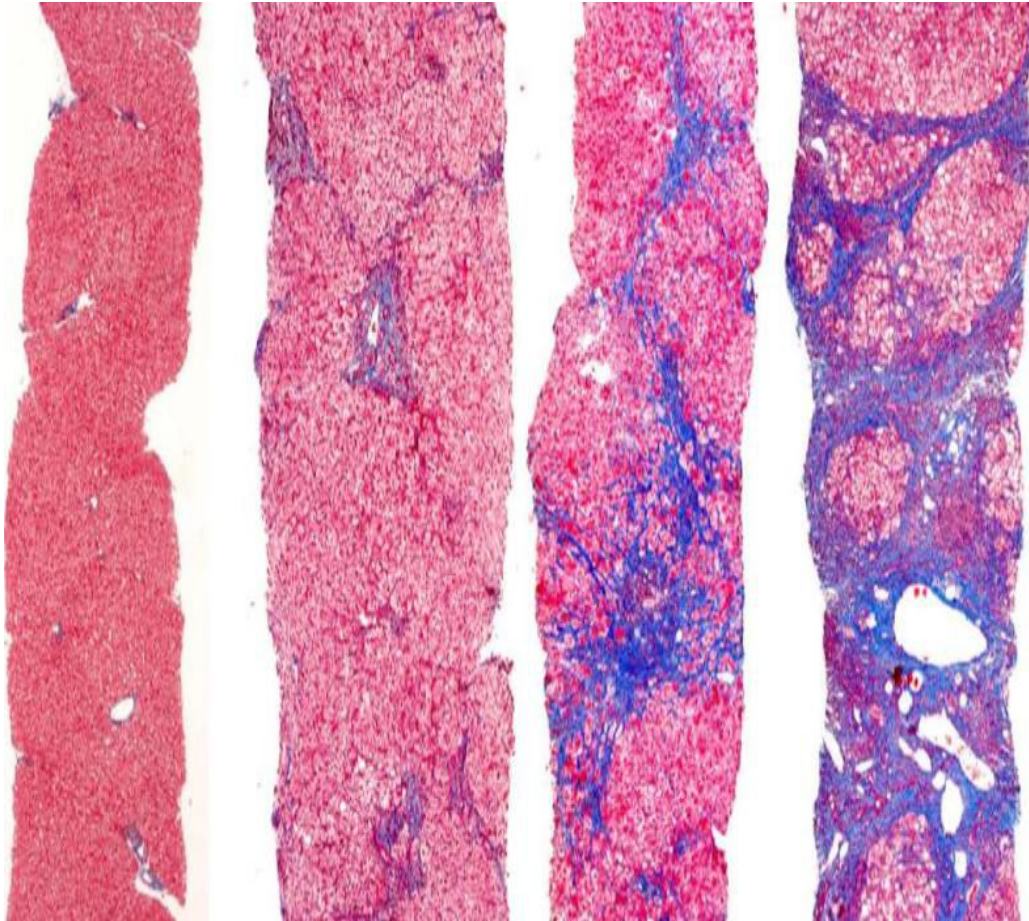


6 years AFTER SVR

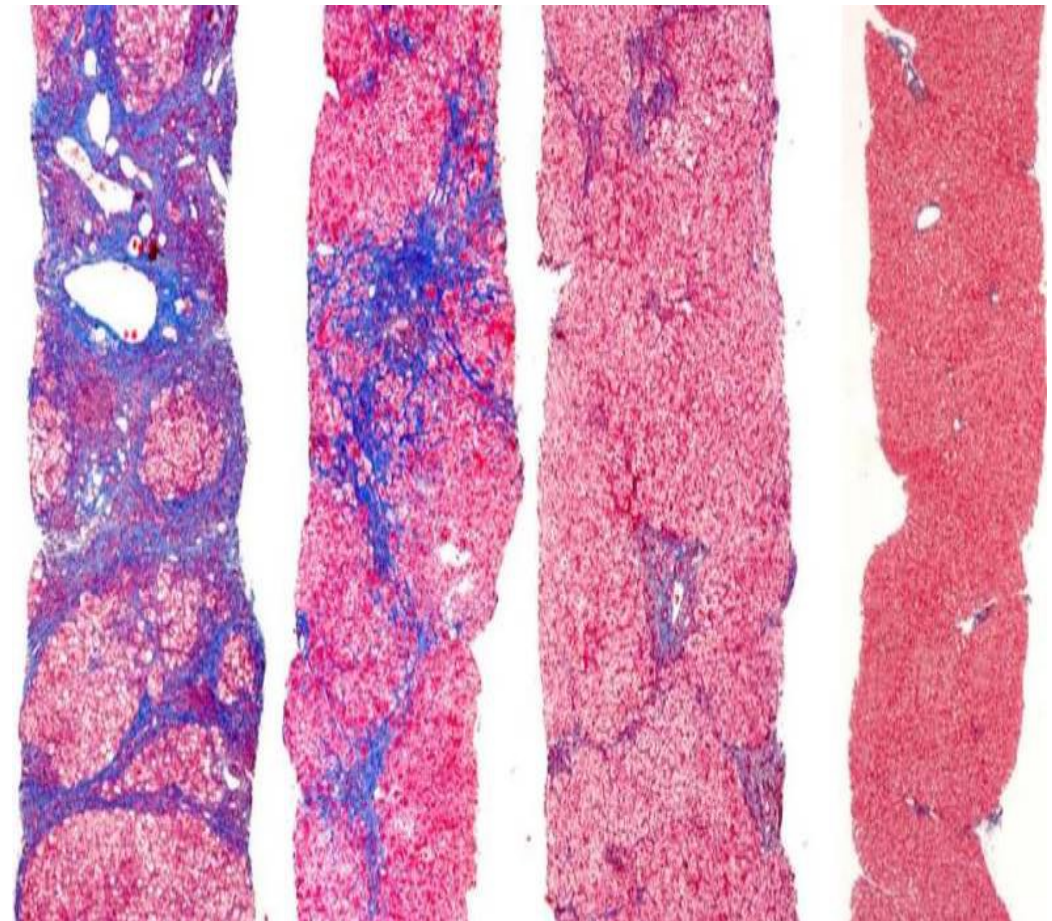


Evolution of fibrosis in chronic viral hepatitis

Natural History →



Treatment →



Regression of fibrosis / cirrhosis

Questions pending

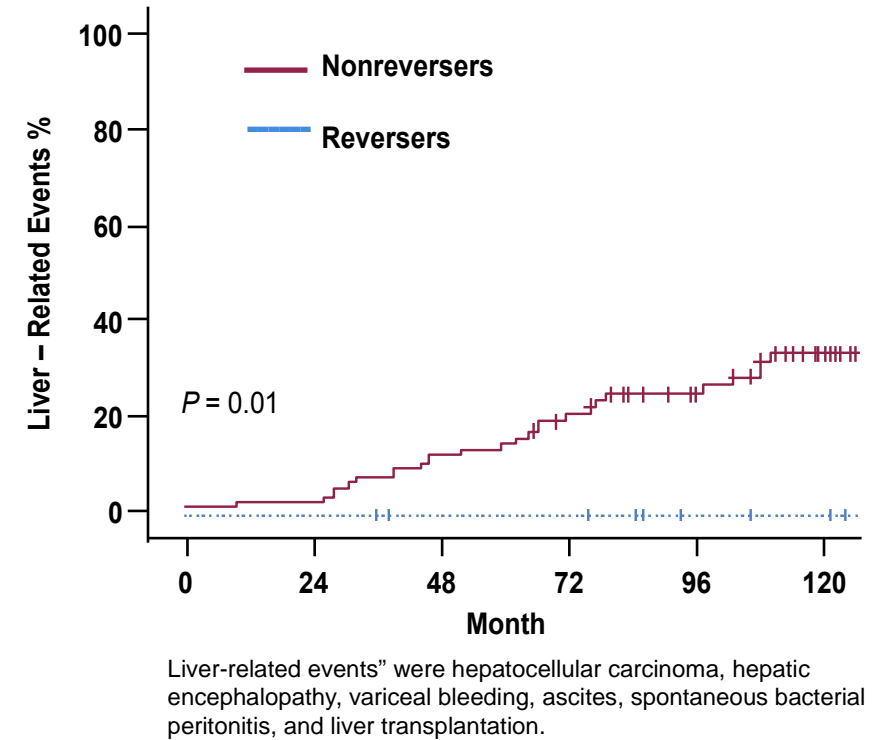
- Is histological regression of cirrhosis clinically relevant ?
- Which cirrhosis may regress after viral eradication/suppression ?
- How to evaluate fibrosis regression ?

Clinical relevance of histological regression

The relationship of regression of cirrhosis to outcome in Hep C

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

- 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 annual incidence of LRE was 0% 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



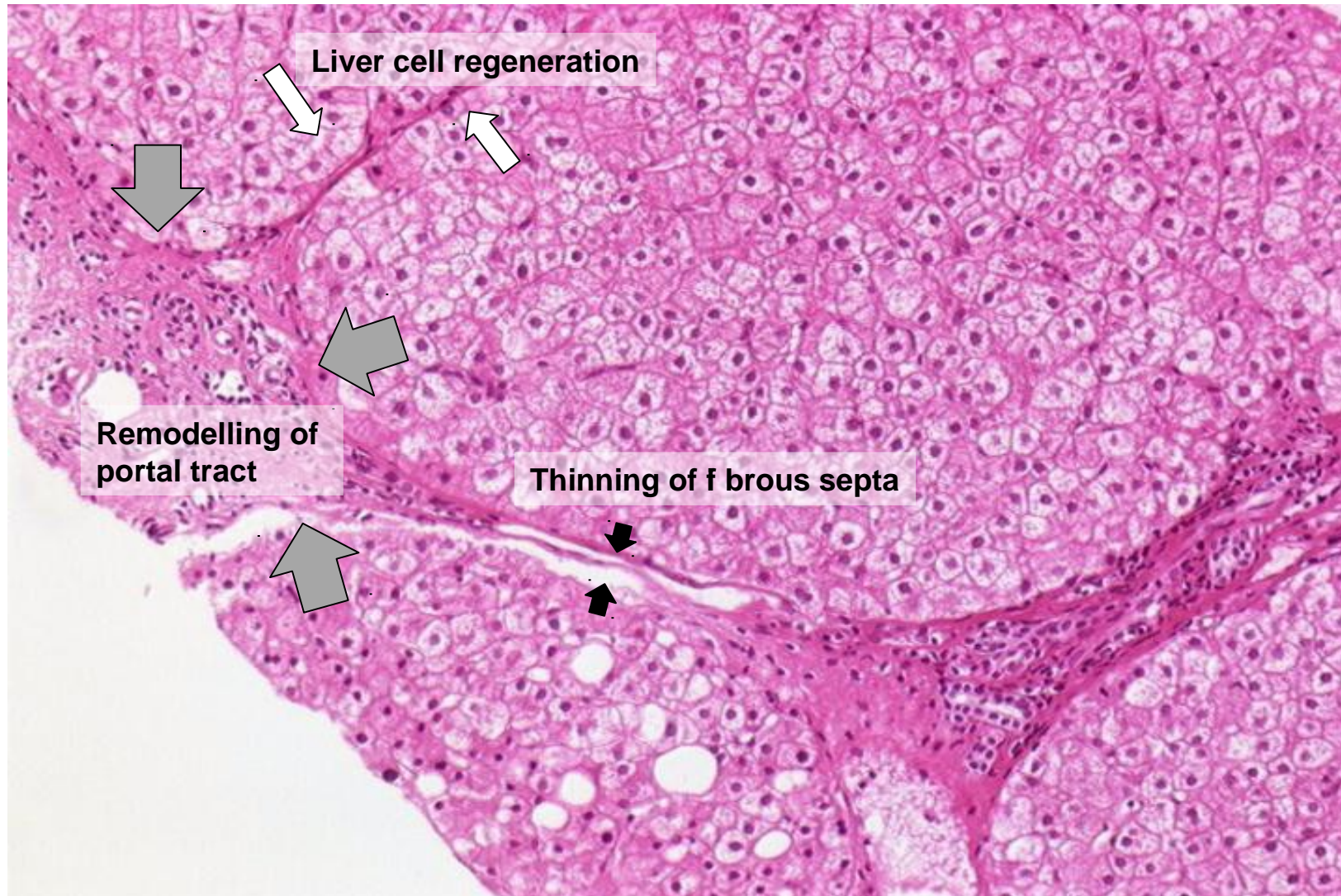
Adapted from Mallet V, *et al. Ann Intern Med* 2008; 149:399-403

Regression of cirrhosis is associated with decreased liver-related morbidity

clinical relevance to assess fibrosis/cirrhosis regression

Which cirrhosis may regress ?

Pathophysiology of cirrhosis regression



Liver Biopsy, 6 years after SVR

Which cirrhosis may regress ?

1. Thinning of fibrous septa : Enzymatic degradation of fibrous septa :

Early cirrhosis

2. Reshaping of portal tract : Persisting portal vessels and central veins within annular fibrous tissue

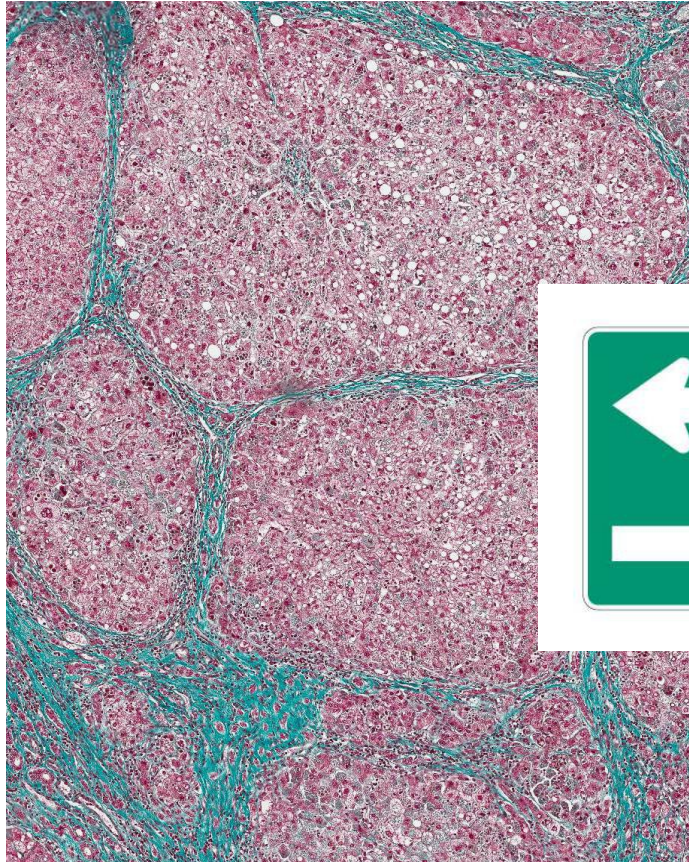
Absence of extensive vascular thrombosis

3. Hepatocyte regeneration : arrest of necroinflammation

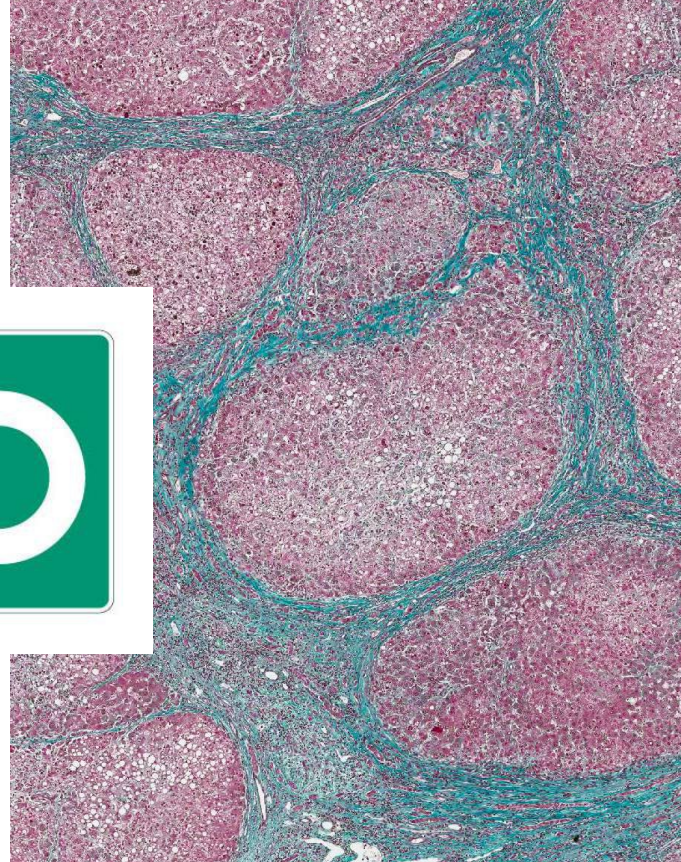
To treat the etiology of the disease

Laennec score of cirrhosis

4a



4b



4c



- Thin fibrous septa
- Regenerative nodules

- 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

How to assess cirrhosis/fibrosis regression ?

Liver biopsy ?

Non invasive markers ?

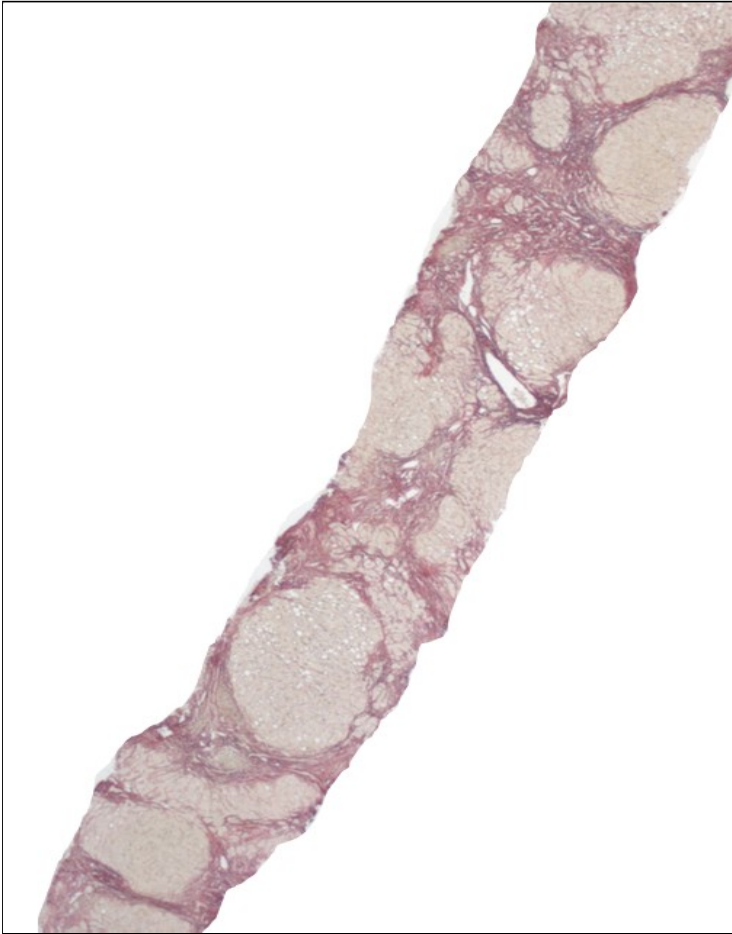
How to assess cirrhosis/fibrosis regression ?

Liver biopsy

- Histological staging system defined for stable or progressing fibrosis, not for regressing cirrhosis
- Specific histological features of regressing fibrosis not included in scoring systems
- Sampling error in regressing fibrosis unknown

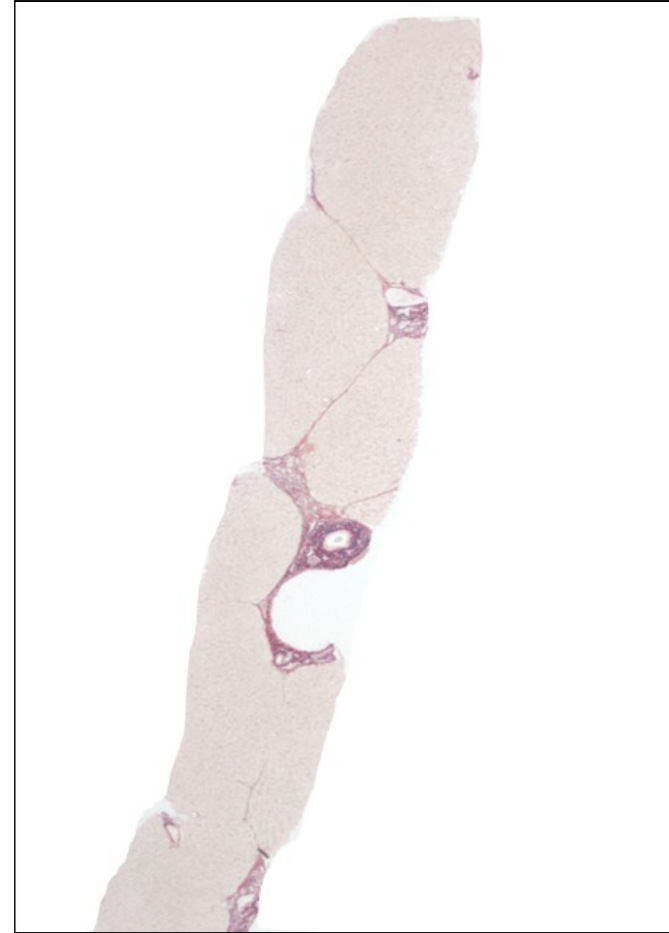
Mr B... F, cirrhose C

Avant Ttmt : F4



Score Laennec : F4 b

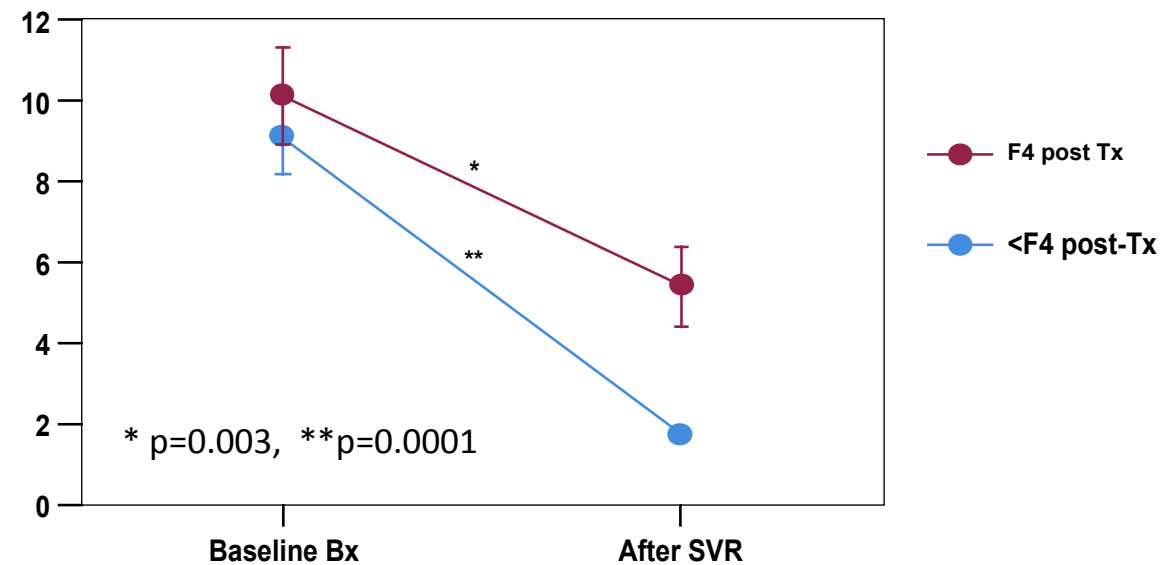
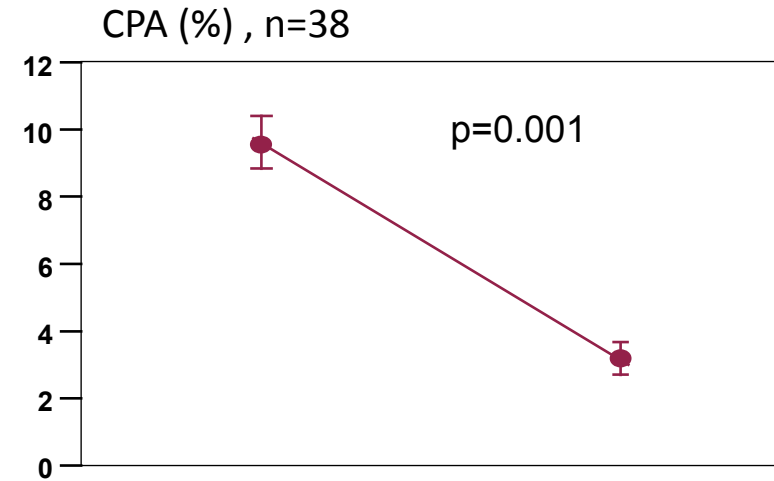
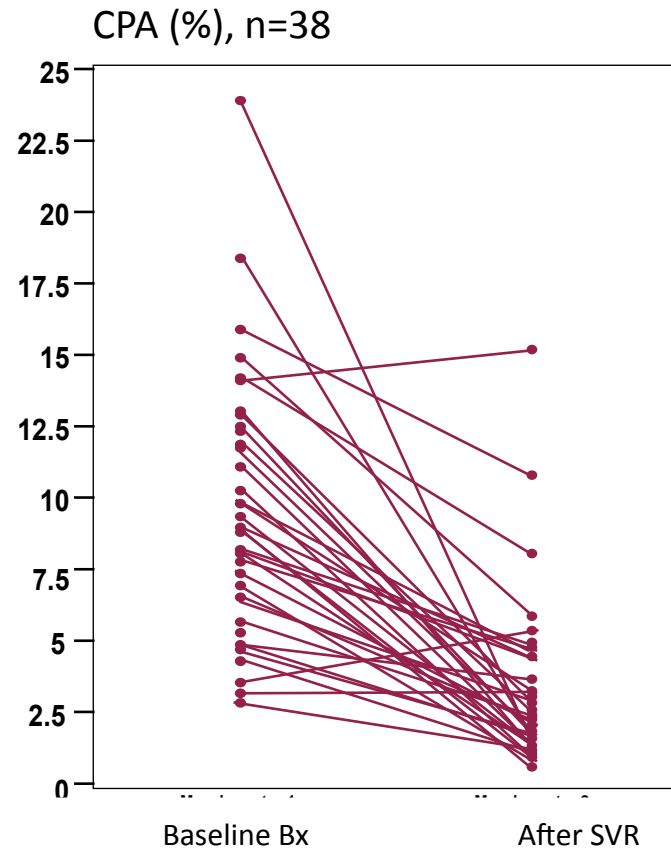
6 ans après traitement et SVR: F4



F4a



Collagen Proportional area (morphometry) Comparison before and after SVR



How to assess cirrhosis/fibrosis regression ?

Non invasive markers

- Serum markers : defined with liver biopsy with stable or progressing fibrosis, not with regressing fibrosis
- Fibroscan, serum markers : role of confounding histological features (regression of necroinflammation)

How to assess regression of liver fibrosis/cirrhosis after antiviral treatment

Answer : ??

Comments ?

Questions ?