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Liver Cancer Screening
with a Focus on Hepatitis C

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Who is This Guy, Exactly?

- Most hep C treatment in the US has historically been provided by gastroenterologists
- The Viral Hepatitis Clinic at KPHI was started in 2004, and is staffed entirely by Kaiser Permanente's Infectious Diseases team
- To avoid any confusion, here are 3 easy clues that I'm not a gastroenterologist:
  - **I typically approach patients from the front when introducing myself**
  - **If you see flecks of brown on my shoes — no worries, that's just chocolate or coffee. All good!**
  - **I drive a Nissan Leaf**

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Hepatitis C Virology as it Relates to Cancer Risk

Quick, Easy, and Relevant Virology

- Most viruses that cause cancer integrate themselves in some way into your DNA — HIV (a retrovirus) and hepatitis B (a DNA virus) are great examples
- Hep C is a single-stranded RNA virus. It does not become a part of your DNA, and is not innately oncogenic as a virus
- But hep C does scar the liver in many patients, and once a liver is very scarred (cirrhotic) from **any** cause, liver cancers can arise out of the blue
- 6 main hep C genotypes: Geno 1 is most common in the US. Geno 3 patients are at greater risk for steatosis and cirrhosis (and thus liver CA) than other genotypes. An ‘extra’ reason to treat your Genotype 3 patients!

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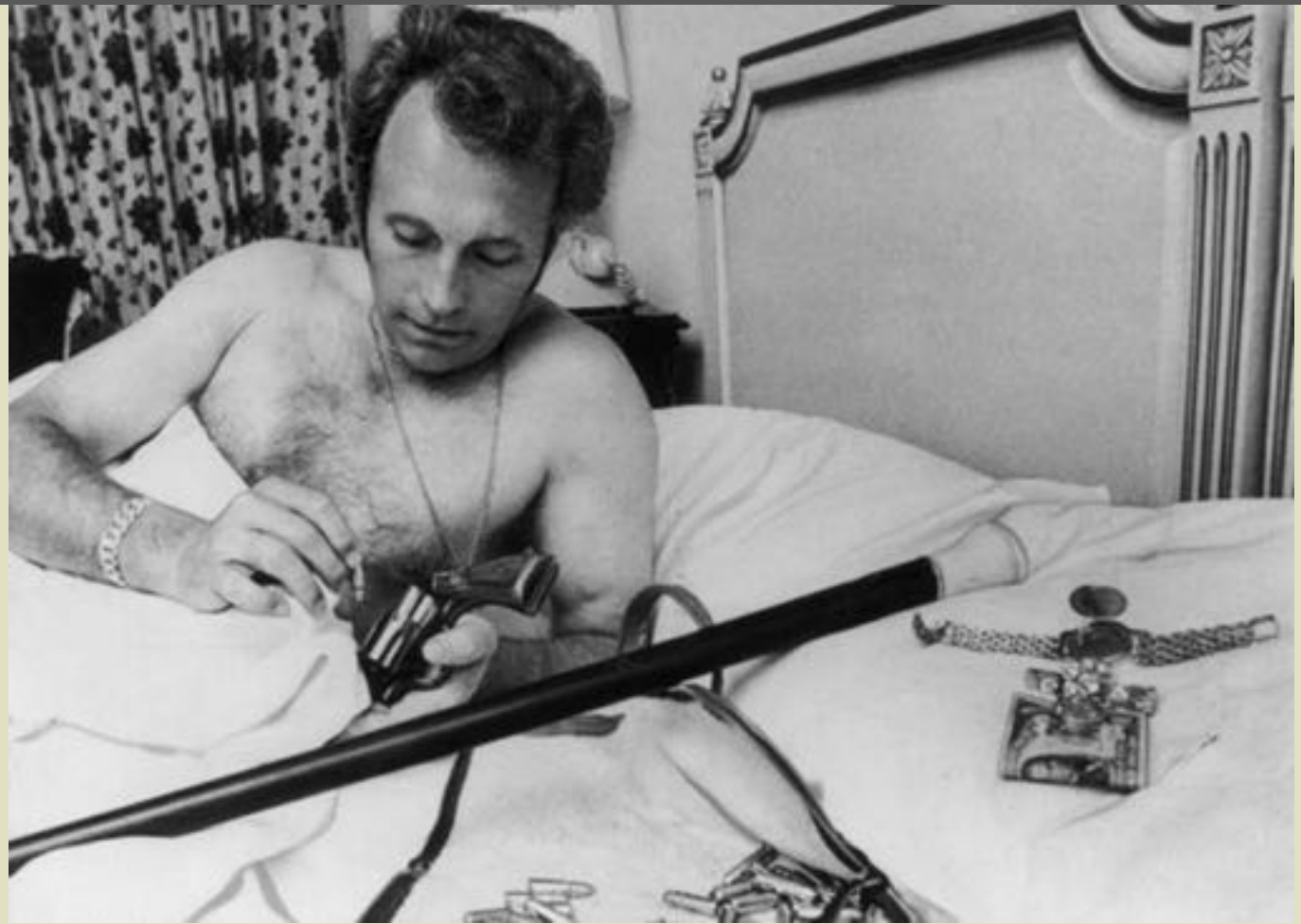
Hep C Infection: Natural History



HCV and Progressive Liver Disease: Who and How Fast?

About 20% (not everyone!) of those with chronic hepatitis C will develop cirrhosis, usually over the course of several decades.

Many pts with HCV will **not** accrue significant liver damage over their lifetime. For these patients, hep C is largely a background issue in their health.

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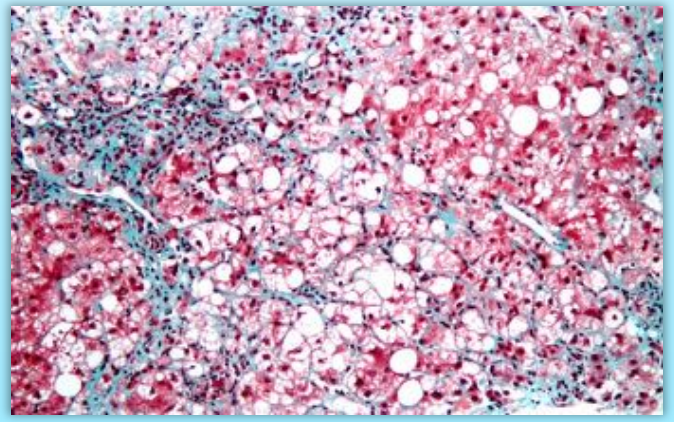
Four Co-factors in Who Becomes Cirrhotic from HCV



HCC Screening: Rationale and Effectiveness

Does Liver Cancer Screening Work?

- The effectiveness of HCC screening is limited, due to both the lethality of the cancer itself and the limitations of current our screening tests
- Among the best data supporting HCC screening comes from a large, randomized Chinese trial of hep B patients in 2004*: US and AFP Q6 mos decreased mortality by 27% over 5 years
- A 2022 meta-analysis of 59 studies suggests screening patients with cirrhosis for HCC provides a 23% decrease in mortality**
- So — it's no slam dunk, but yes, screening the right patients for liver cancer is important and can save lives

*Zhang BH et al. Randomized controlled trial of screening of hepatocellular carcinoma. J Cancer Res Clin Oncol 2004; 130:417..
**Singal AG et al. HCC Surveillance improves early detection, curative treatment receipt, and survival in patients with cirrhosis: a meta-analysis. J Hepatol 2022; 77: 128

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What's the Goal of Liver Cancer Screening, Exactly?

- Not as obvious a question as it sounds!
- Liver cancer's a beast — 5-year survival is still south of 20% in most studies. **However:**
  - This is in large part because of the frequency with which HCC is diagnosed in advanced stages
  - HCC treatments are advancing steadily, and should bend the survival curve
- So, the goal of liver cancer screening is specifically to detect EARLY liver cancers — 2 CM or smaller, without invasion — when the whole range of treatments is open to our patients. For patients with *early* liver CA, 5-year survival exceeds 70%.

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Why Screen Every 6 Months, by the Way?

- The recommendation for a 6-month screening interval is based on **how fast** HCC grows — its median doubling time as a tumor (around 120 days)
- Observational effectiveness and survival data support Q 6-month screening:
  - a randomized trial of Q3 vs Q6 month screening showed similar rates of HCC detection.* Meaning, Q3 month screening was no better.
  - a retrospective study comparing Q6 vs Q12 mo screening in cirrhotic pts diagnosed HCC showed 50% longer survival in those who received Q6 mo surveillance--30 vs 45 mos.** So, Q6 mos was better than Q12 mos.
- Because a 6-month surveillance interval is based on tumor doubling time rather than on the RISK of developing HCC, we **don't** screen more frequently for those at higher risk of HCC than others

* Trinchet JC et al. Ultrasonographic surveillance of hepatocellular carcinoma in cirrhosis: a randomized trial comparing 3- and 6-month periodicities. Hepatology 2011; 54: 1987.
** Santi V et al. Semiannual surveillance is superior to annual surveillance for the detection of early hepatocellular carcinoma and patient survival. J Hepatol 2010; 53: 291.

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So – WHOM Should We Screen for HCC?

- The AASLD (‘23) and EASL (‘18) guidelines and expert opinion coalesce around the same groups who should be offered HCC screening:
  - **Pts with Child-Pugh A and B (non-decompensated) cirrhosis**
    - *This includes both HCV-infected pts and those CURED of hep C*
  - **Pts with Child-Pugh C (decompensated) cirrhosis ONLY IF they are awaiting liver transplantation**
  - **Subsets of patients with hepatitis B who do NOT have cirrhosis**
    - I won’t get into this here (remember: HBV’s innately oncogenic)
- **Dealer’s choice?: HCV-infected patients with F3 fibrosis**
  - EASL guidelines and many US clinics — including ours — recommend screening for this group, though current AASLD guidelines do not.

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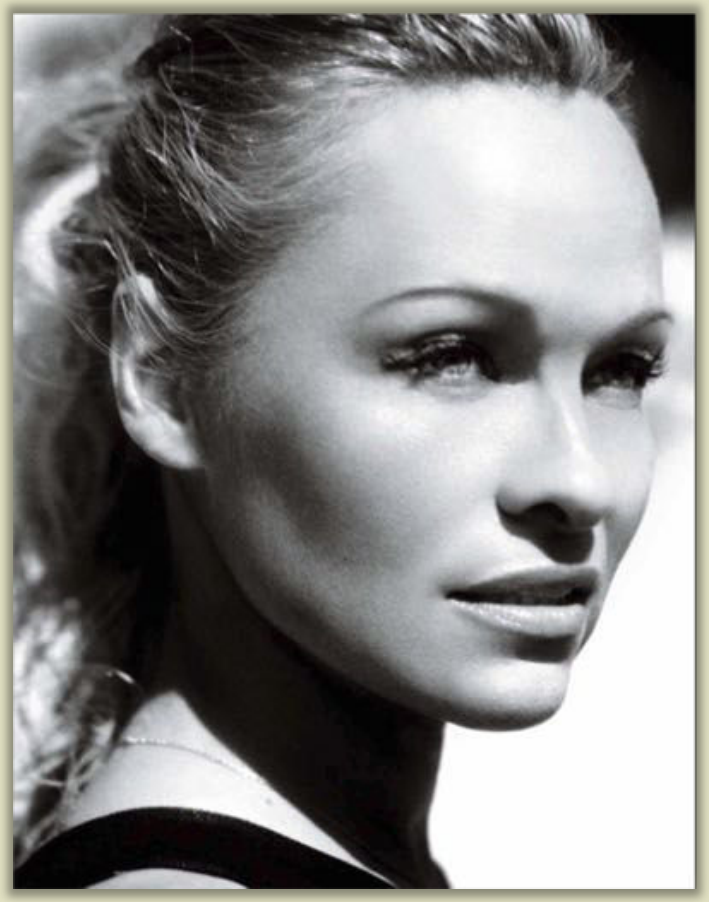
HCC Screening: The Tests We Use



HOW Should We Screen for Liver Cancer?

- **An HCC-screening abdominal (liver) ultrasound every 6 months is the backbone of liver cancer screening**
  - Estimated sensitivity for finding liver cancer by ultrasound is ~80% overall: 45% for early-stage HCC, and ~85% for lesions >4 cm
  - CT imaging, MRI, and contrast-enhanced US are all more sensitive than US for HCC detection — but cost, radiation (CT), and feasibility/capacity concerns have kept these in the background for now

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Liver Cancer Screening Tests, cont'd

- **Serum AFP (alfa-fetoprotein) every 6 months should be included w/ultrasound-based HCC screening**
  - After decades of debate, Q6 month AFP is now recommended in the 2023 AASLD guidelines, along with Q6 month ultrasounds
  - AFP testing adds about 15% sensitivity for HCC detection relative to US alone
  - However, AFP lacks both sensitivity and specificity. AFP can be elevated for many reasons other than liver cancer — liver inflammation from viral hepatitis, decompensated cirrhosis, pregnancy, and other cancers (testicular, ovarian, gastric, etc.)
  - SO — adding AFP testing to Q6-month USs has upsides (increased cancer detection) and downsides (cost, wild goose-chases, patient inconvenience and distress). Regardless, this is now part of AASLD recs.

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So, to Review:

- **For hep C-infected/-cured patients with cirrhosis (who don't have decompensated liver disease):**
  - Q6 month liver ultrasounds and AFPs (needn't be on the same day) is the current AASLD recommendation to screen for HCC
  - If a pt declines AFP testing (cost, inconvenience, needle phobia, whatever): Q6 month US alone is certainly reasonable, but definitely document that you've recommended Q6 mo AFPs
- **For hep C-infected/-cured patients with F3 fibrosis:**
  - AASLD guidelines don't suggest HCC screening is needed, but many US clinics (including ours!) do this for F3 HCV pts, and it's standard in Europe

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Easy-peezy! Now Let's Do Some FAQs

FAQs

Does this mean I should try and figure out the fibrosis stage of everyone I'm seeing who has hep C infection?

- **Yup, within reason, that's prudent.** Many non-invasive options for estimating liver fibrosis exist, with varying cost: AST-to-platelet-ratio (APRI), Fib-4, Fibrotest, shear-wave elastography (SWE). Do your best, think about cost, and don't go crazy. Liver biopsies are NOT necessary for HCC screening decision-making.

If my patient is cured of hep C, but had underlying cirrhosis, can I stop HCC screening?

- **Nope!** Patients cured of hep C do decrease their rates of liver cancer — but some risk remains, even many years after cure. **So HCC surveillance should be continued indefinitely in those w/advanced fibrosis, even after SVR/cure of hep C**

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More FAQs

If I see a new lesion on a screening US but it's small — under 1 CM — and the AFP is normal, what should I do?

- Lesions under 1 cm are too small to biopsy or be definitively characterized on MRI or CT
- **Hence, a short-interval US and AFP in 3-4 months is a common approach** Depending on what that shows: consider MRI vs reverting to Q6 mo USs.

If I see a new lesion on a screening US that's, say, 1.5 CM, and a normal AFP — what then?

- New liver lesions 1 CM or bigger should be taken seriously, even with a normal AFP. Remember — we are trying to find early HCC!
- **Further imaging — an MRI, ideally** (MRIs are more accurate than CTs for HCCs under 3 cm), or a 3-phase, contrast CT scan, is the next step. **Don't sleep on a new liver lesion that's 1 CM or bigger!**

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FAQs About AFP

If I see a new 2 cm liver lesion on US but the AFP is normal, is the normal AFP good news for the patient? Can I breathe easier?

- **Nope!** About 80% of patients with early liver cancer have normal AFPs. **AFPs should NEVER be used to "rule out" an HCC**

What if my patient has a clean US but an elevated AFP? Argh!

- **Everything depends on how high the AFP is (>20?), and on the clinical situation (is the cirrhosis longstanding? Does the pt smoke? Any family history of liver cancer?)**
- **Consider an MRI or a short-interval f/u US/AFP (e.g., 3 mos)**, and at least think about other causes of AFP elevation (pregnancy, ovarian / testicular / other CA) that might merit evaluation

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More FAQs About AFP

Is there an AFP level above which I should really start to be worried?

- Much depends on baseline AFPs and trends in any given individual. **But an AFP level above 20 ng/ml is common threshold above which to pay close attention.** Above 100 ng/ml is very worrisome. Above 400 ng/ml in a high-risk liver patient is nearly diagnostic of HCC.

If my patient says, "Can I please just do an AFP every 6 months without the ultrasound?", what's a good reply?

- "Do you ever call Boston's Pizza and just order a handful of pepperoni, but no pizza?"
- **Checking AFPs by themselves, in place of liver imaging, is not an acceptable means of screening for liver cancer. Don't go there.**

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Final Thoughts

Let's Not Forget the Point of Hep C Treatment

Please Keep Curing Your Patients of Hep C!

- Curing hepatitis C causes **regression** of liver fibrosis in many patients
  - Even cirrhosis (prior to the development of portal hypertension) can occasionally regress, though this takes years
- **Cure reduces the risk for liver failure, liver cancer, and improves lifespan**. And, of course, it prevents spread to others!
- Whether cured of hep C or not, if you do have a patient with advanced liver fibrosis, screen them carefully for liver cancer—Q6 month ultrasounds and AFP checks—and you'll save some lives

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Thanks for your hard work and for your attention

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