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We Should Stop HCC Surveillance Selectively in Virologically Cured HCV Patients With Advanced Fibrosis and Cirrhosis Pre-Treatment

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UNIVERSITY OF MIAMI

Disclosures

- Research grant support from Gilead, Merck, and AbbVie for research related to transplanting organs from hepatitis C-infected donors into hepatitis C-negative patients.

Why Do We Perform HCC Surveillance in Patients With Cirrhosis?

- Per AASLD 2018 Guidelines[1]
  - Cirrhosis is biggest risk factor for HCC
    - 85-90% of cases in Western populations due to cirrhosis
  - HCC incidence rate historically “substantial” in patients with cirrhosis: 2-4% per year
  - Survival highly dependent on stage of disease
    - 70% 5-year survival for early stage
    - 5-10% 5-year survival for advanced stage
    - Retrospective data (meta-analysis)
      - Patients undergoing surveillance: 50.8% 3-year survival
      - Patients without prior surveillance: 29.7% 3-year survival
  - Surveillance tools are inexpensive, non-invasive, and have moderate performance

1-Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. *Hepatology.* 2018;68(2):723-750.

Key Caveats to HCC Surveillance Guidelines for Patients With Cirrhosis

- No RCTs in Western populations with cirrhosis
- All data on benefit of surveillance based on retrospective observational data
  - Potential for bias in studies in that patients who undergo surveillance inherently different and cannot be fully account for
- Guidelines have historically been based on the benefit of surveillance when the annual incidence of HCC was 1.5%[1,2,3]
  - 1.5% threshold based on modeling study from 1996
    - Estimated surveillance cost-effective if 1.5% incidence
    - Cost of $26,000-$55,000 for each additional life-year gained[3]

1-Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. *Hepatology.* 2018;68(2):723-750;
2-Bruix J, Sherman M. Management of hepatocellular carcinoma. *Hepatology.* 2005;42(5):1208-1236;
3-Sarasin FP, Giostra E, Hadengue A. Cost-effectiveness of screening for detection of small hepatocellular carcinoma in western patients with Child-Pugh class A cirrhosis. *Am J Med.* 1996;101(4):422-434.

What Is the Baseline HCC Incidence Rate in Patients With HCV Cirrhosis

5-yr incidence of 13.4%[1]

GT 1b: 4.3% per year
GT 2: 1.7% per year%[2]

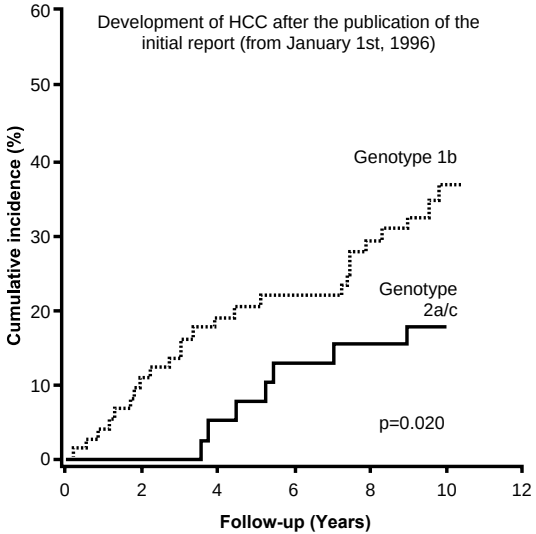
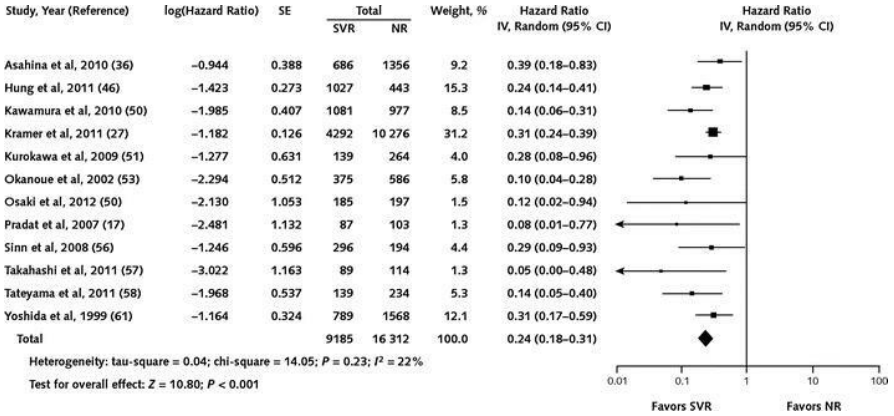


Fig. 2 Cumulative incidence of HCC in 127 patients with cirrhosis according to the HCV genotype

1-Degos F, Christidis C, Ganne-Carrie N, et al. Hepatitis C virus related cirrhosis: time to occurrence of hepatocellular carcinoma and death. *Gut.* 2000;47(1):131-136; 2-Bruno S, Crosignani A, Maisonneuve P, Rossi S, Silini E, Mondelli MU. Hepatitis C virus genotype 1b as a major risk factor associated with hepatocellular carcinoma in patients with cirrhosis: a seventeen-year prospective cohort study. *Hepatology.* 2007;46(5):1350-1356.

Impact of SVR on Risk of HCC

- No RCTs evaluating impact of SVR on incident HCC
- Meta-analysis of 18 studies with adjusted effect estimates[1]
- Pooled adjusted HR of benefit of SVR on incidence of HCC
  - All HCV-infected patients: 0.24 [95% CI, 0.18 to 0.31], moderate-quality evidence
  - HCV + advanced liver disease:, 0.23 [CI, 0.16 to 0.35], moderate-quality evidence)



Study, Year (Reference)	log(Hazard Ratio)	SE	Total SVR	Total NR	Weight, %	Hazard Ratio IV, Random (95% CI)
Asahina et al, 2010 (36)	−0.944	0.388	686	1356	9.2	0.39 (0.18–0.83)
Hung et al, 2011 (46)	−1.423	0.273	1027	443	15.3	0.24 (0.14–0.41)
Kawamura et al, 2010 (50)	−1.985	0.407	1081	977	8.5	0.14 (0.06–0.31)
Kramer et al, 2011 (27)	−1.182	0.126	4292	10 276	31.2	0.31 (0.24–0.39)
Kurokawa et al, 2009 (51)	−1.277	0.631	139	264	4.0	0.28 (0.08–0.96)
Okanoue et al, 2002 (53)	−2.294	0.512	375	586	5.8	0.10 (0.04–0.28)
Osaki et al, 2012 (50)	−2.130	1.053	185	197	1.5	0.12 (0.02–0.94)
Pradat et al, 2007 (17)	−2.481	1.132	87	103	1.3	0.08 (0.01–0.77)
Sinn et al, 2008 (56)	−1.246	0.596	296	194	4.4	0.29 (0.09–0.93)
Takahashi et al, 2011 (57)	−3.022	1.163	89	114	1.3	0.05 (0.00–0.48)
Tateyama et al, 2011 (58)	−1.968	0.537	139	234	5.3	0.14 (0.05–0.40)
Yoshida et al, 1999 (61)	−1.164	0.324	789	1568	12.1	0.31 (0.17–0.59)
Total			9185	16 312	100.0	0.24 (0.18–0.31)

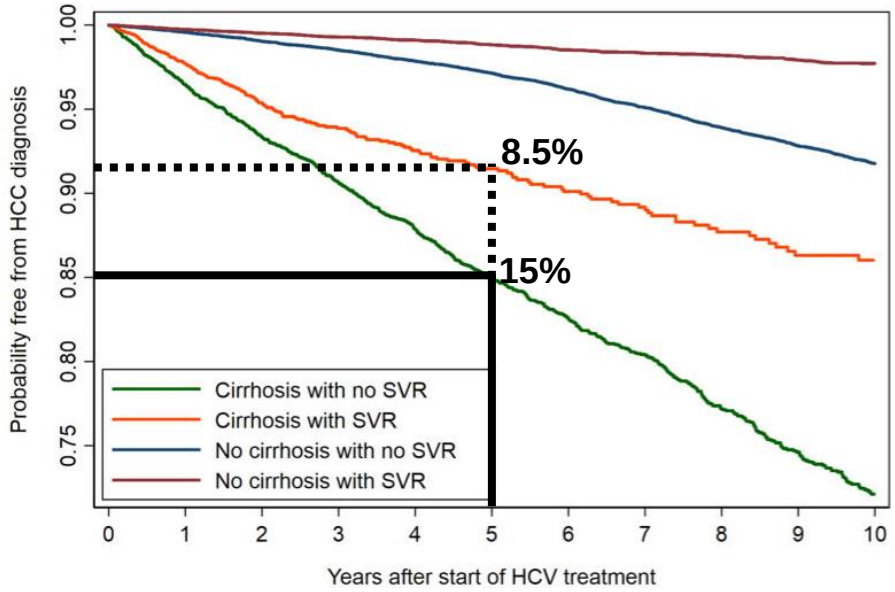
Heterogeneity: tau-square = 0.04; chi-square = 14.05; $P = 0.23$; $I^2 = 22\%$

Test for overall effect: $Z = 10.80$; $P < 0.001$

1-Eradication of Hepatitis C Virus Infection and the Development of Hepatocellular Carcinoma. *Annals of Internal Medicine.* 2013;158(5_Part_1):329-337.

Annual Incidence of HCC in Patients With HCC Cirrhosis and SVR

a. **ALL TREATMENTS: Kaplan-Meier curves of survival free of HCC by cirrhosis and SVR status after antiviral treatment.**



Ioannou GN, Green PK, Berry K. HCV eradication induced by direct-acting antiviral agents reduces the risk of hepatocellular carcinoma. *Journal of hepatology.* 2017.

Is Continued HCC Surveillance Really Cost Effective?

- Microsimulation model of natural history of HCV and HCC in patients with SVR
- Base case is 50 y/o with biannual surveillance with US + AFP
  - HCC incidence in cirrhosis: 1.95% per year
  - HCC with advanced fibrosis: 0.58% per year
- Results:
  - Cirrhosis
    - ICER (stopping age 70): $93,587 per QALY
    - ICER (stopping age 75): $223,364 per QALY
    - Stopping age 70: QALY gains of 51 per 1,000 patients at additional cost of $2,694,400
  - Advanced fibrosis
    - ICER (stopping age 65): $98,800 per QALY
    - ICER (stopping age 77): $129,781 per QALY
  - Surveillance vs no surveillance per 1,000 patients with cirrhosis
    - Surveillance: 389 HCC cases detected; 82 VE,150 E, 157 Int/Advanced
    - No surveillance: 381 HCC cases detected (incidental or through symptoms); 9 VE, 93 E, 239 Int/Advanced

1-Mueller PP, Chen Q, Ayer T, et al. Duration and cost-effectiveness of hepatocellular carcinoma surveillance in hepatitis C patients after viral eradication. *Journal of hepatology.* 2022.

Is Continued HCC Surveillance Really Cost Effective?

- Key considerations in interpreting data
  - Transplant probability and waiting time used pre-2020 data[1]
    - Median waiting time in models: 237.4 days
    - Median waiting time per 2020-2021 data: 287 days
- Sensitivity analysis
  - For compensated cirrhosis individuals, the cost-effective surveillance strategy was most sensitive to the likelihood of incidental detection of HCC, the progression rate from early-stage HCC to intermediate/advanced stage HCC, and overall survival following palliative care.
  - DAAs reduce HCC incidence but what about risk of tumor progression[2]
    - Cohort study evaluating risk of recurrence and disease progression with SVR after HCC curative treatment
    - DAA therapy significantly associated with lower risk of tumor progression: 0.28 (0.13-0.61): $p<0.001$
- Total cost (can't focus just on CE)
  - 100,00 patients with cirrhosis + SVR: 5100 QALYs at cost of $269,440,000
  - 1,000,000 patients with cirrhosis + SVR: 51,000 QALYs at cost of $2,694,400,000

1-Mueller PP, Chen Q, Ayer T, et al. Duration and cost-effectiveness of hepatocellular carcinoma surveillance in hepatitis C patients after viral eradication. *Journal of hepatology.* 2022; 2-Ikenaga H, Uchida-Kobayashi S, Tamori A, et al. Direct-acting antivirals reduce the risk of tumour progression of hepatocellular carcinoma after curative treatment. *Journal of viral hepatitis.* 2022;29(1):52-59.

Why We Should Not Continue HCC Surveillance

- Lower yield due to changing incidence and progression:
  - Incidence of HCC with SVR dramatically lower
  - Progression from early to intermediate to late stage slower so likelihood of diagnosing at earlier stage higher
- Costly
  - Cost effectiveness based on higher CE threshold and many assumptions that may not be correct
  - Cost effectiveness at individual level and not on overall healthcare system
- Burden to healthcare system
  - Finite number of ultrasound machines, techs, etc.
- Improving therapies for late stage
  - Rapidly evolving field with improved systemic therapies that narrow survival gap between early vs intermediate vs late stage

1-Mueller PP, Chen Q, Ayer T, et al. Duration and cost-effectiveness of hepatocellular carcinoma surveillance in hepatitis C patients after viral eradication. *Journal of hepatology.* 2022; 2-Ikenaga H, Uchida-Kobayashi S, Tamori A, et al. Direct-acting antivirals reduce the risk of tumour progression of hepatocellular carcinoma after curative treatment. *Journal of viral hepatitis.* 2022;29(1):52-59.

HCC Surveillance after Virologically Cured HCV Patients With Advanced Fibrosis and Cirrhosis Pre-Treatment DON'T STOP!

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Disclosures

- Grant/Research Support
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- Principle Investigator for a Drug Study
  - Merck/Eisai, Exelixis
- Consultant
  - Bayer, Eisai, Merck, Genentech
- Speakers Bureau
  - Bristol Meyers Squibb, Gilead, Abbvie, Eisai, Salix, Exelixis, Genentech, Intercept (all resigned as of 6/1/2021)
- Advisory Board Membership
  - Eisai, Exelixis, Genentech, Astra Zeneca

I will not discuss any off label therapies

All Society Guidelines Agree: Continue Surveillance After SVR

American Gastroenterological Association Institute Clinical Practice Update—Expert Review: Care of Patients Who Have Achieved a Sustained Virologic Response After Antiviral Therapy for Chronic Hepatitis C Infection

Ira M. Jacobson,[1] Joseph K. Lim,[2] and Michael W. Fried[3]

[1]Department of Medicine, Mount Sinai Beth Israel Medical Center, Icahn School of Medicine at Mount Sinai, New York, New York; [2]Section of Digestive Diseases and Yale Liver Center, Yale University School of Medicine, New Haven, Connecticut; and [3]Division of Gastroenterology and Hepatology, UNC Liver Center, University of North Carolina School of Medicine, Chapel Hill, North Carolina

BPA 4: Surveillance for HCC with liver imaging ± serum AFP should be pursued twice annually for an indefinite duration in all patients with stage 3 fibrosis or liver cirrhosis post-SVR.

AASLD AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C

IDSA Infectious Diseases Society of America

Surveillance for hepatocellular carcinoma is recommended for patients with cirrhosis,[a] in accordance with the AASLD guidance on the diagnosis, staging, and management of hepatocellular carcinoma.	Strong, Moderate[b]

EASL Clinical Practice Guidelines:
Management of hepatocellular carcinoma

The limited data produced so far showed that HCC occurrence is not eliminated in patients at risk, at least in the short/mid-term after SVR of HCV with DAA, mandating continued surveillance.[68,112–114]

PRACTICE GUIDANCE | HEPATOLOGY, VOL. 68, NO. 2, 2018

Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases

Jorge A. Marrero,[1] Laura M. Kulik,[2] Claude B. Sirlin,[3] Andrew X. Zhu,[4] Richard S. Finn,[5] Michael M. Abecassis,[2] Lewis R. Roberts,[6] and Julie K. Heimbach[6]

- **The risk of HCC for patients with HCV-related cirrhosis who develop SVR after DAA treatment is lowered, but not eliminated, and therefore patients with cirrhosis and treated HCV should continue to undergo surveillance.**

EASL recommendations on treatment of hepatitis C: Final update of the series☆

European Association for the Study of the Liver*

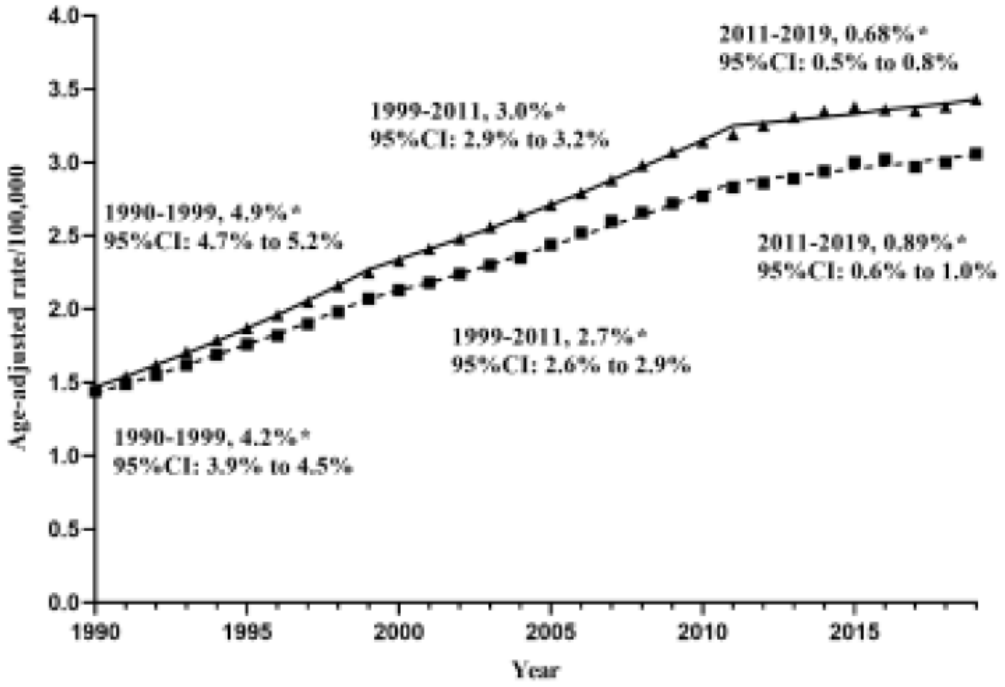
- In patients with advanced fibrosis (METAVIR score F3) and cirrhosis (METAVIR score F4), surveillance for HCC must be continued because an SVR will reduce, but not abolish, the risk of HCC (**A1**).

What is the Purpose of Surveillance?

- Reduce mortality by early detection and early treatment
- Reduce the severity of a condition by identifying that condition and offering effective treatment
- Increase choice by identifying condition at an early stage when more options are available

WHO: Screening Programs, a Short Guide 2020, accessed Feb 2022

HCV-Related HCC Is Still a Problem in the US



C. Liver cancer due to hepatitis C

Han et al, Hepatology 2022

Journal Pre-proof

HCC Surveillance Improves Early Detection, Curative Treatment Receipt, and Survival in Patients with Cirrhosis: A Systematic Review and Meta-Analysis

HCC surveillance is associated with improved early detection, curative treatment receipt and overall survival in patients with cirrhosis

Surveillance for HCC remains controversial due to lack of randomized data

Articles from 2014-2020
Inclusion: Surveillance benefits and harms in patients with cirrhosis

Systematic Review/Meta-Analysis:
59 Studies with 145,396 patients

HCC Surveillance associated with:

Early stage detection:
OR 1.86, 95%CI 1.73 – 1.98

Receipt of curative therapy:
OR 1.83, 95%CI 1.69 – 1.97

Overall survival:
HR 0.67, 95%CI 0.61 – 0.72

Surveillance Harms:
4 studies with 2,578 patients

Occurred in **8.8% - 27.5% of patients across studies**

Most mild in severity

Lack of data on financial or psychological harms

JOURNAL OF HEPATOLOGY
The Home of Liver Research

Singal et al, JHep 2022

Numerous Models Developed or Studied to Attempt to Predict HCC Risk After SVR

- FIB-4/APRI
- Liver Elastography
- Various combinations of lab data and imaging data
- Multivariable Risk Calculators
  - HCC Risk Calculator
  - aMAP Risk Score
- “Deep Learning” Machine algorithms
- Biomarkers
  - Specific protein based signatures (eg. ANGPT2, VEGF)
  - Gene expression (eg. Oncogenes, stellate cell activation)
  - Epigenetics (eg. H3K27ac)
  - Combination of these with AFP or other clinical markers

None have been validated well enough to be included in guidelines
None have been shown to identify a group that has zero risk
Most (if not all) underestimate the risk of HCC development

Towards personalized screening for hepatocellular carcinoma: Still not there

Vincenza Calvaruso[1,*], Jordi Bruix[2]

F3? F4? Maybe even F2?

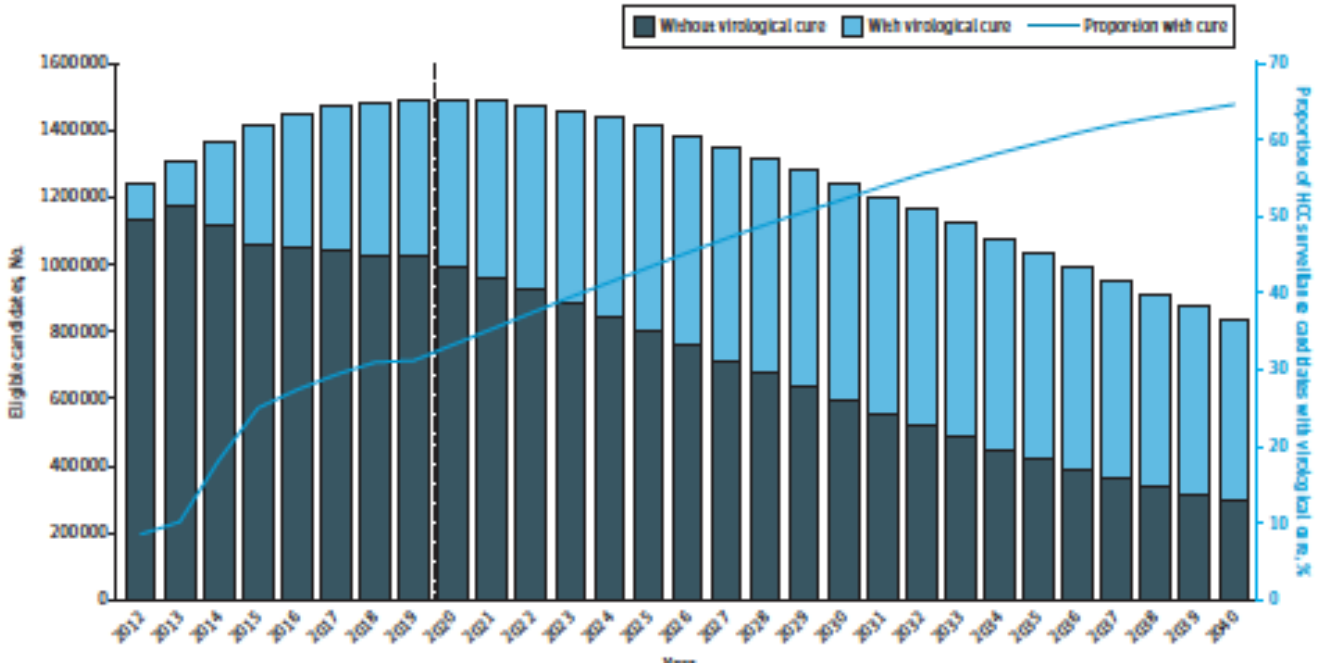
- Liver biopsy is gold standard for determining fibrosis stage
- BUT, most patients now are staged with non-invasive testing
- Non-invasive testing is imperfect, and may over- or under-estimate stage of fibrosis (and even less accurate after SVR)
- Many patients may be misclassified for screening based on fibrosis stage
- (and don’t forget that fibrosis reversal ≠ HCC risk decrease)

Ioannou GN, JHep 2021

Who is the population?

- Number of HCV candidates for HCC surveillance is decreasing in US

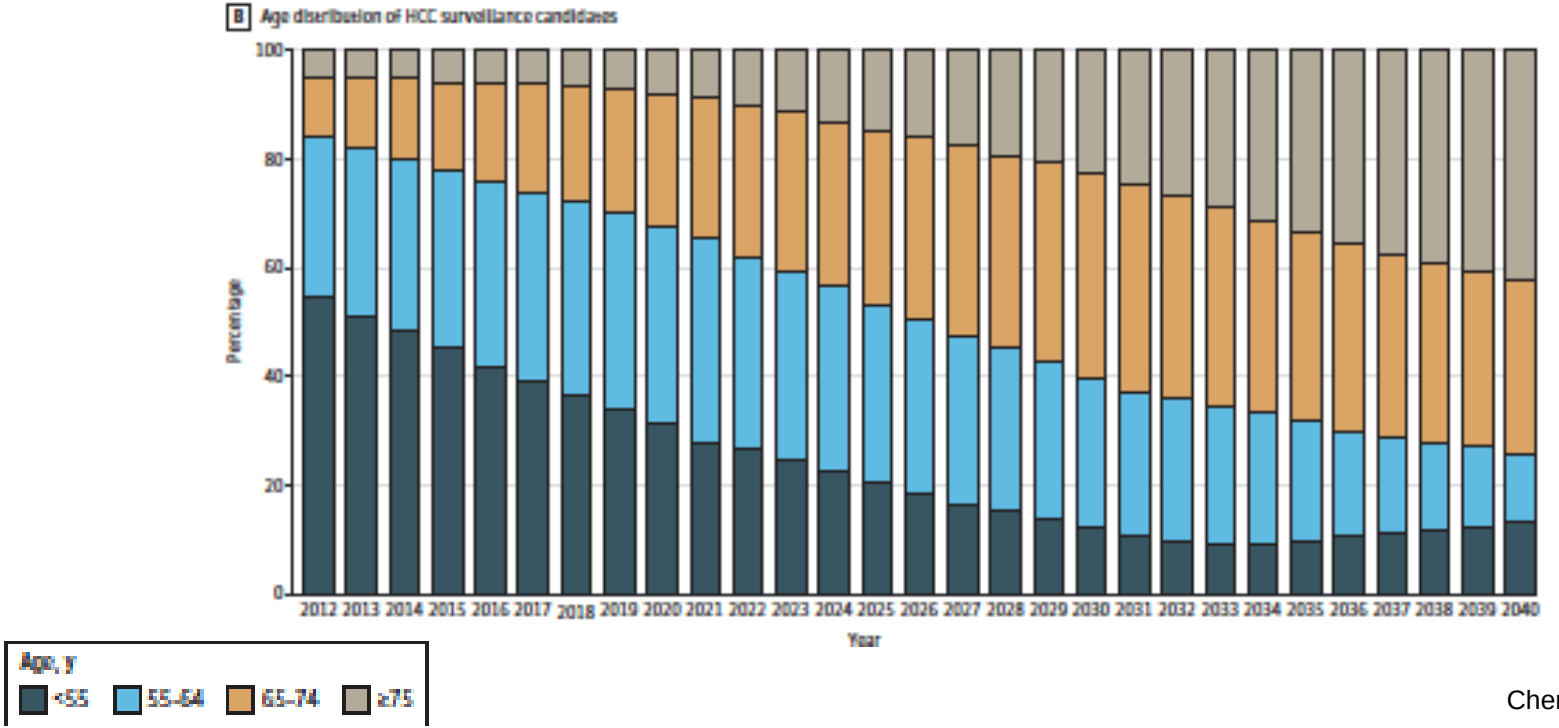
Figure 2. Projection of Number of Candidates for Hepatocellular Carcinoma (HCC) Surveillance by Cure Status From 2012 to 2040



Chen et al, JAMA Open 2020

Who is the population?

- Many candidates for surveillance will “age out” or develop other comorbidities



Chen et al, JAMA Open 2020

What is the risk of HCC development in F3/F4 patients?

- Cirrhosis: 1.95 per 100 person-years
- Advanced fibrosis: 0.58 per 100 person-years
  - This is only based on two studies, and more data is needed
- So is it cost effective to screen at this incidence?

Mueller et al, JHep 2022

HCC Incidence Threshold for Routine Surveillance is Much Lower in Hepatitis C after SVR

Objective

- The AASLD guidance recommends biannual surveillance for (HCC) in individuals with cirrhosis if HCC incidence is above 1.5 per 100 person-years (PY); however, this threshold is unknown for individuals ***who achieved virological cure***. Our objective was to estimate this HCC incidence threshold in cirrhosis patients.

Methods

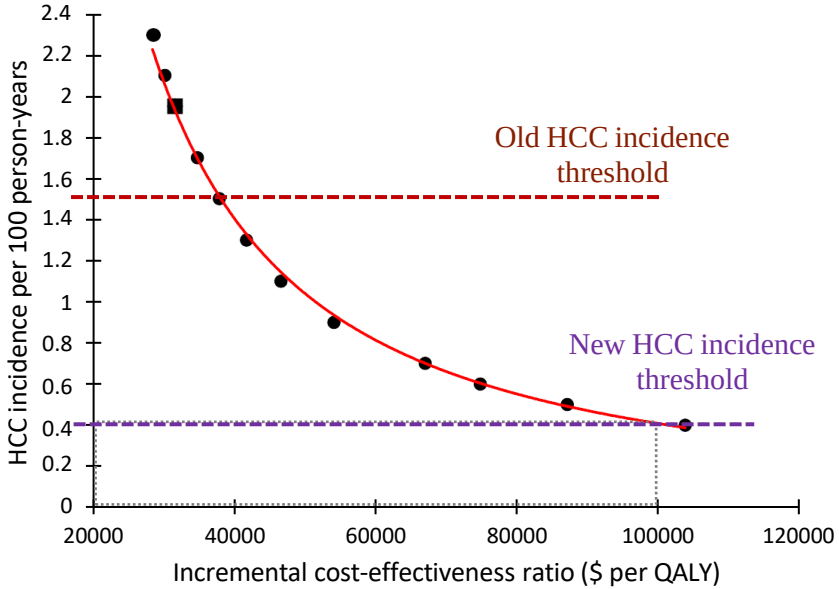
- A microsimulation model of the natural history of HCC in individuals with HCV and cirrhosis who achieved virological cure with oral direct-acting antivirals (DAAs)

Main Findings

- Using the recommended willingness to pay threshold of $100,000 per quality-adjusted life year, HCC surveillance could be cost-effective if the annual incidence rate of HCC exceeds 0.41%, which is much lower than the previous 1.5% incidence used to guide HCC surveillance decisions

Conclusions

- Our study provides an important update on HCC incidence threshold above which routine HCC surveillance is cost-effective in individuals with HCV cirrhosis who achieved cure with DAAs.



Chhatwal J, et al., Abstract 28.

Cost Effectiveness of HCC Surveillance after SVR

- Most recent cost effectiveness study suggested that surveillance in cirrhosis cost effective to age 70 and surveillance in bridging fibrosis cost effective to age 60
- However, this study admits that the data from their model in advanced fibrosis is poor as there is limited data on incidence of HCC in advanced fibrosis

- They did NOT include systemic therapy as a treatment option in their model
  - And 239 patients (63%) would be diagnosed at stage for systemic therapy, but they modeled for these patients to get ablation/TACE

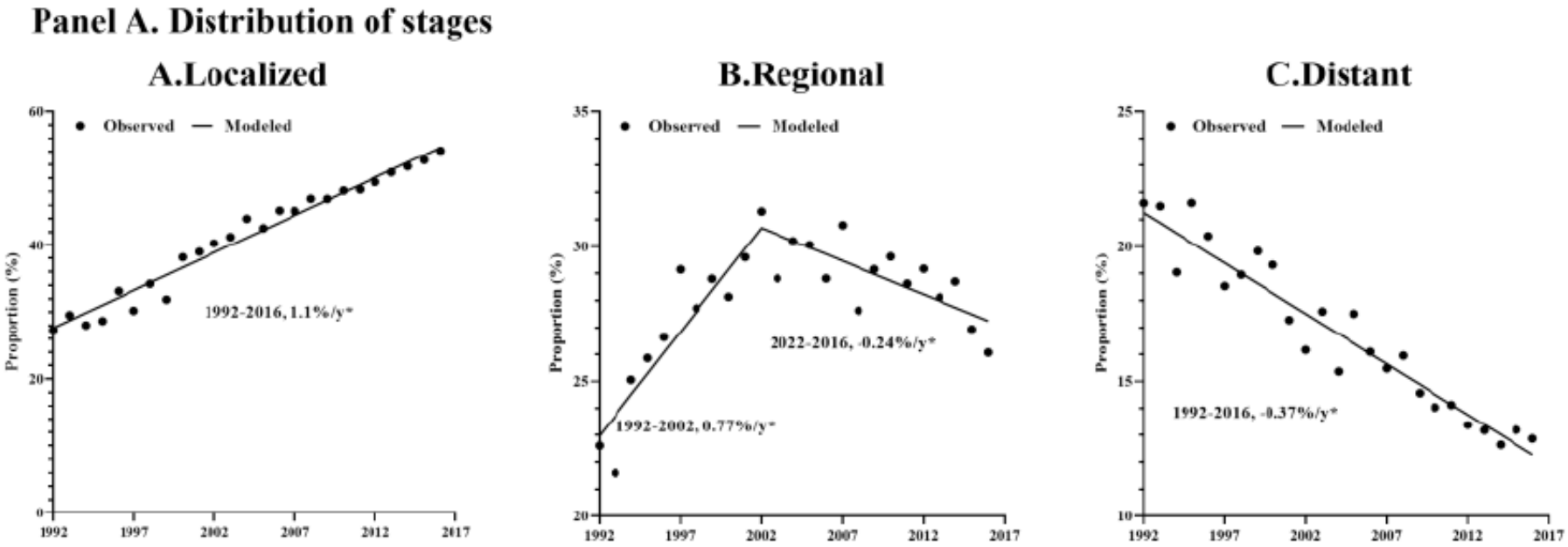
Mueller et al, JHep 2022

Diagnosis of HCC at Advanced Stage is Expensive

- First line treatment: atezolizumab plus bevacizumab
  - ~$22,000 per month just for the drugs
- In IMBRAVE150 trial: median duration of treatment was 7.4 months with atezo, 6.9 months with bev
  - Median OS 19.2 months
- One treatment course of atezo/bev $154k just for drugs
- Then there is treatment of infusions, repeated clinic visits, multiple lab draws, repeated imaging, AEs, hospitalizations, second line therapies….

Finn et al, NEJM 2021

We Have Been Improving the Proportion of Patients Diagnosed at Localized Stage: Do we really want to give that up?

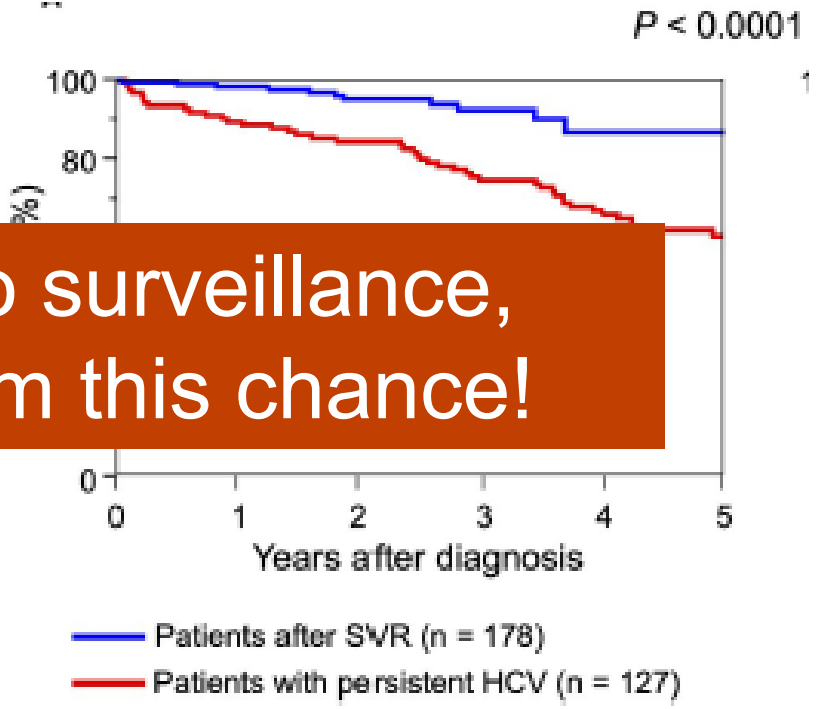


Han et al, Hepatology 2022

De Novo HCC after SVR vs before SVR

- Patients who develop HCC after SVR have
  - Better overall survival
  - [illegible] treatment for recurrences
  - Improved liver function
    - Which in turn allows further treatments if needed

But if we don't do surveillance, we don't give them this chance!



Toyoda et al, Hepatol Comm 2021

Conclusions

- Even after SVR, HCC risk remains and surveillance should NOT STOP
- Clinical parameter risk models thus far have failed in stratifying patients well enough to stop surveillance in a subgroup
  - Biomarkers are needed to aid in risk stratification
- Patients who have achieved SVR who develop HCC have a better overall prognosis, which increases the clinical benefit and cost effectiveness of surveillance
- Even with advances in systemic therapy, earlier diagnosis is better in order to cure rather than palliate