CHRONIC LIVER DISEASE 2016

Joe Alcorn MD

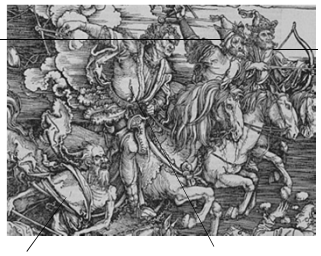
Ignoring

Because Rx of Hep C is getting easier and easier…

Chronic Liver Disease

- We ask the fellows to note:
  - Compensated vs Decompensated?
  - MELD?
  - OLT Candidate?
  - Health Maintenance
    - Vaccinations
    - Risk for Varices?
    - Risk for HCC addressed?
    - Can we alter fibrogenesis?

The Consequences ….



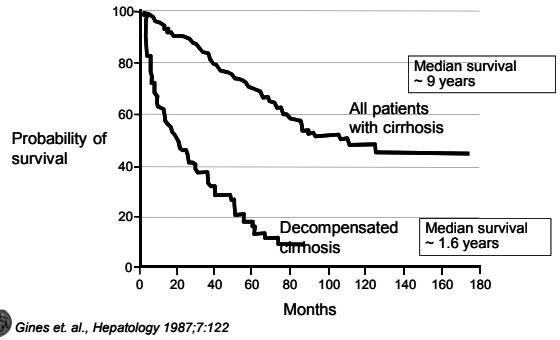
Child's Class – the None/Little or Alot Scale

Child's Class	Points	1 Yr survival	2 Yr Survival
A	5-6	100	85
B	7-9	80	60
C	10-15	45	35

INR <1.7 > 2.3
Bilirubin < 2 > 3
Albumin < 2.8 > 3.5
Ascites and HE : none/a little/alot

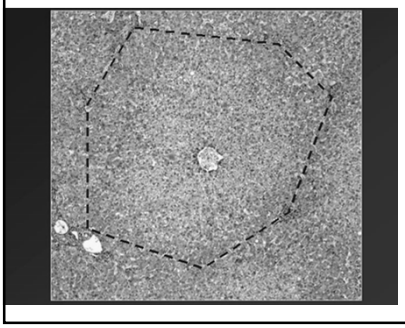
SURVIVAL TIMES IN CIRRHOSIS

Decompensation Shortens Survival



Gines et. al., Hepatology 1987;7:122

Classic Lobule



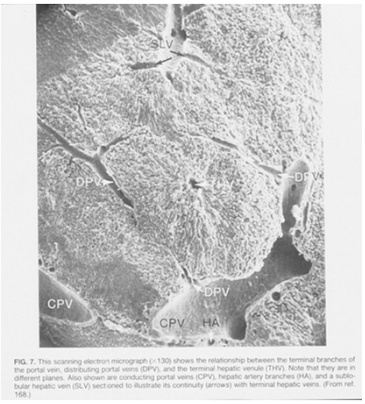


FIG. 7. This scanning electron micrograph (×130) shows the relationship between the terminal branches of the portal vein, distributing portal veins (DPV), and the terminal hepatic venule (THV). Note that they are in different planes. Also shown are conducting portal veins (CPV), hepatic artery branches (HA), and a sublobular hepatic vein (SLV) sectioned to illustrate its continuity (arrows) with terminal hepatic veins. (From ref. 168.)

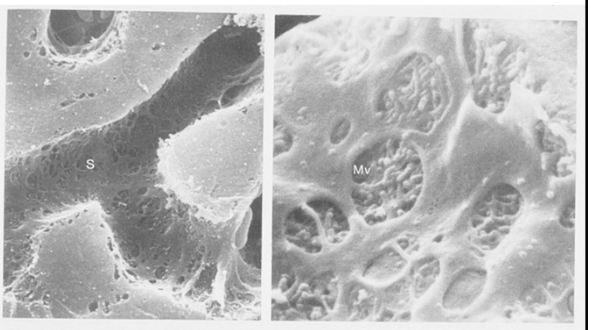
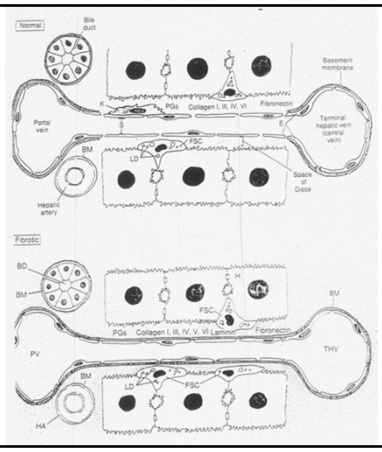
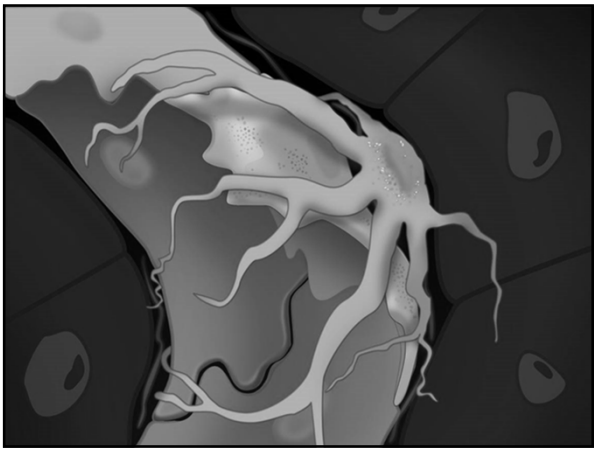
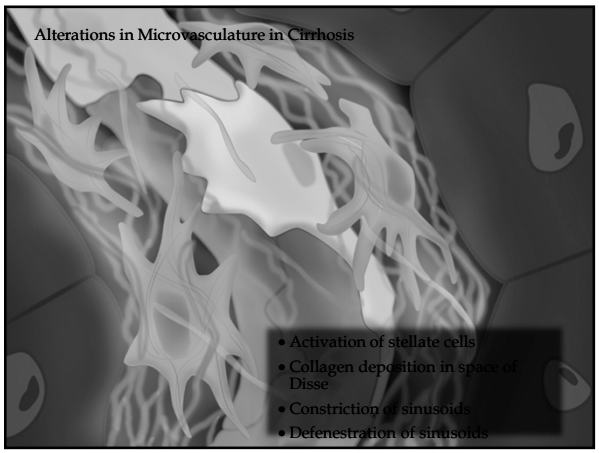
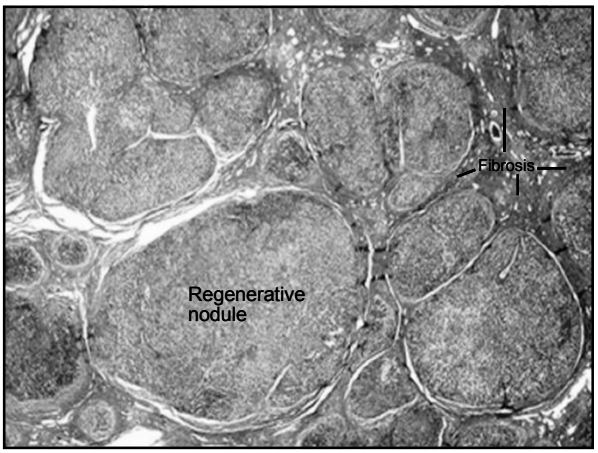


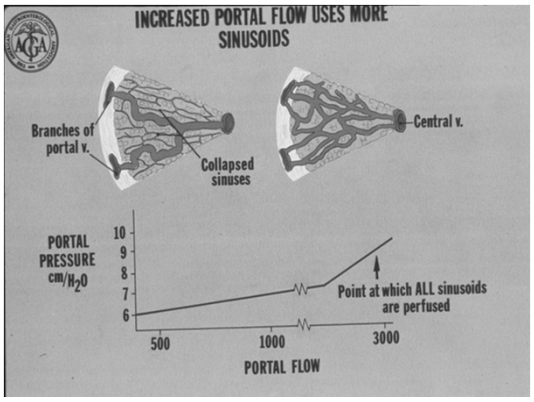
FIG. 6. Hepatic sinusoids. **Left:** These scanning electron micrographs of sinusoids (S) show the multiple and varying-sized fenestrations in the endothelial lining cells (×3,585). **Right:** Further enlargement (×12,725) shows the microvilli (Mv) of underlying hepatocytes readily exposed to the sinusoidal contents. (From ref. 168.)

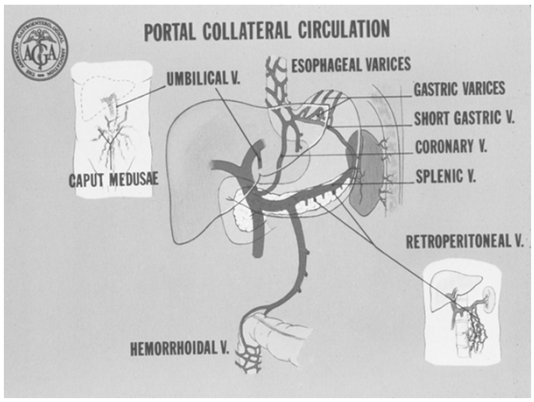












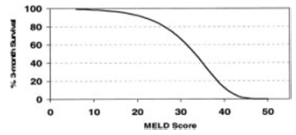
Treatment of Decompensation…

- Blood shunting around liver – HE
- Blood diverted through collaterals – bleeding
- Backpressure on splanchnic circulation - ascites
- Lactulose and Rifaximin – NO need to measure NH4
- Screening for Varices; non-selective Beta Blockade vs Ligation
- 2 gram Na+ diet plus Furosemide/spironol actone 40/50

When to Transplant?

- One year mortality post-op – 10%
- How can you tell which cirrhotic patients have a one year survival rate < 90?
- For every patient obtaining a graft there are others who don't get that graft.
- Therefore in addition to a duty to the patient, there is a duty to society…

Survival and MELD Score



3 Month Mortality :
MELD score > 40 : 71.3% mortality
MELD score 30–39 : 52.6% mortality
MELD score 20–29 : 19.6% mortality
MELD score 10–19 : 6.0% mortality
MELD score < 9 : 1.9% mortality

When do you think about OLT?

- Consider it and reference it in your notes as soon as you recognize chronic liver disease
- Line up referral as soon as you have:
  - Mid-teen MELD AND
  - No absolute contraindications

  It can take months to line up non-urgent evaluation…

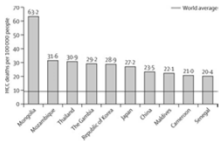
Cirrhotic are 1) Compensated or not
2) Prognosis Scored – MELD
3) OLT Candidates or not…
4) Other modifiable risks?
5)How do we alter Natural Hx?

HCC – epidemiology

see NEJM 2011 364:1118; Lancet 2012 379:1245

- Third most common cause of cancer death
- >780,000 diagnoses/yr Annual Review Path 2015 10:345
- Rare before 40; peaks at about 70
- Men:Women = 4-5:1
- DM an independent risk Gastro 2004 126:460
- Mortality 5X increased with BMI > 40 NEJM 2003 348:1625
- 77,500$/case in Canada Hepatology 2013 58:1375

Highest HCC prevalence?



Mongolia – Epidemic Hep B AND Hep C Lancet 2011 377:1139

HCC in 2016

- Risk Factors: clearly ongoing active inflammatory liver disease and cirrhosis
- Screening of risk groups identifies early potentially curable disease.
- Cure may occur by resection or ablation…with ongoing HCC risk…
- Cure of HCC AND risk makes Orthotopic Liver Transplantation a crucial consideration

HCC and Risk factors – other causes

HCC INCIDENCE

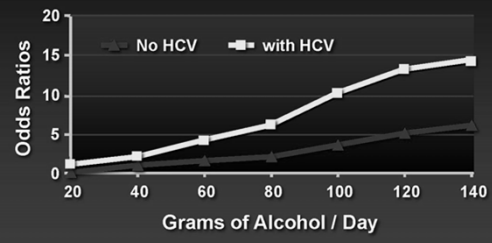
- Stage IV PBC 3-5%/yr
- Cirrhotic Hemochromatosis 1.5%
- Alpha1AT cirrhosis 1.5%
- Cryptogenic cirrhosis 1.5%
- Alcoholic Cirrhosis ? 2%
- NASH Cirrhosis ? 2%
- Wilson's Dz Cirrhosis ?

MULTIPLIERS

- Family History
- Alcohol

CC Epidemiology

Alcohol Intake and the Risk of HCC



onato F, et al, Am J Epidemiol 2002

HCC - Survival

- In the absence of treatment, HCC 5- year overall survival rate is less than 10%.
- But consider the unique problem of a
- malignancy as a late complication of a terminally
- diseased organ…..

Samuel D, Colombo M, El-Serag H, Liver Transplantation, 17:S6-13, 2011

Molecular pathogenesis

- Heterogeneous
- TP53 mutations 25-40%
- CTNNB1 – 25%
- Chromosomal amplifications and deletions common
- Epigenetic suppressor silencing
- Increased EGFR and Ras signaling in 50%
- MTOR disruption – 50%
- Angiogenesis via VEGFA and FGF
- Multiple miRNA signatures
- Hep B DNA integrates into the genome
- Hepatitis C is cytoplasmic only; viral protein activity is complex but does not provide a rate limiting target in carcinogenesis

HCC

A Very Bad Actor

Surveillance – the ONLY RCT

- Randomized Controlled Trial of Screening for Hepatocellular Carcinoma. Zhang BH et al. J Cancer Res Clin Oncol. (2004)

- 18,816 patients with Hep B infection
- 60% adherence to surveillance
- HCC related mortality reduced by 37%
- Mortality due to HCC was significantly lower after five years in the screened group (83 versus 132 per 100,000, mortality rate; ratio of 0.63, 95% CI 0.41-0.98)

If you are waiting for better data…

Fuggedabout it…

Patients no longer allow themselves to be randomized
Poustchi H et al Hepatology 2011;54:1998

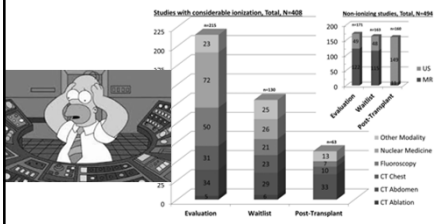
Impact on overall HCC survival hard to define when screening rates are only 20-30% HB El-Serag et al J of Hepatology 2006; 44:158; JA Davila et al Hepatology 2010;52:132

1) Small treatable HCCs represent less than 20% without surveillance, > 70% with surveillance AC Chan et al Ann Surg 2008;247:666
2) Survival rates have increased consistently with surveillance, seemingly due to higher proportion of treatable disease GuiuB et al Clin Gastro Hepatol 2010; 8:986; Anderson KL et al Clin Gastroenterol Hepatol 2008; 6:1418;
3) Patients identified as candidates for and provided loco-regional therapy live longer than those who do not. Llovet JM et al Hepatology 2003; 37:429

Surveillance tests - radiologic

- US- HCC may be echogenic, hypo-echoic or target lesion
  - Sensitivity 65%-80%
  - Specificity >90%
  - Performance characteristics not well defined with nodular livers
  - Difficult in obese
- CT scan – performance characteristics not well defined
  - Experience only in diagnostic /staging studies
  - Radiation exposure and long term cancer risk concerning
- No basis for alternating surveillance modalities
- Twice annual preferred to annual Kim DK et al Hepatology 2007 46:403A

Exposure to ionizing radiation during liver transplantation evaluation, waitlist time, and in the postoperative period: A cause for concern

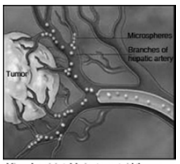


HCC patients exposed to median 137 mSv; Normal background is 2-3 mSv/yr; Nuclear power plant workers are limited to 20 mSv/year in Europe, 50 in the US.

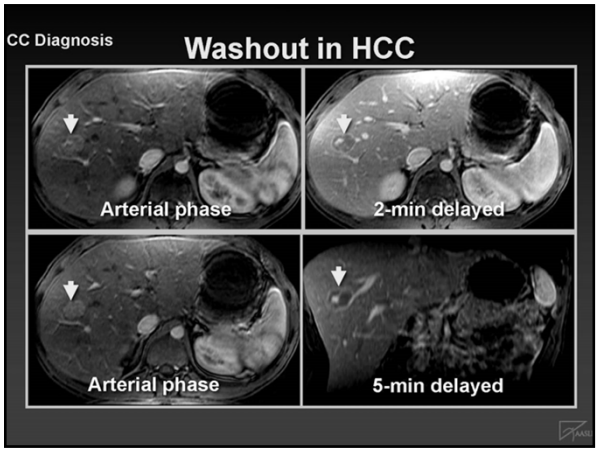
Hepatology
Volume 59, Issue 2, pages 496-504, 20 DEC 2013 DOI: 10.1002/hep.26633
http://onlinelibrary.wiley.com/doi/10.1002/hep.26633/full#hep26633-fig-0003

The Dx of HCC is NEVER made by US alone

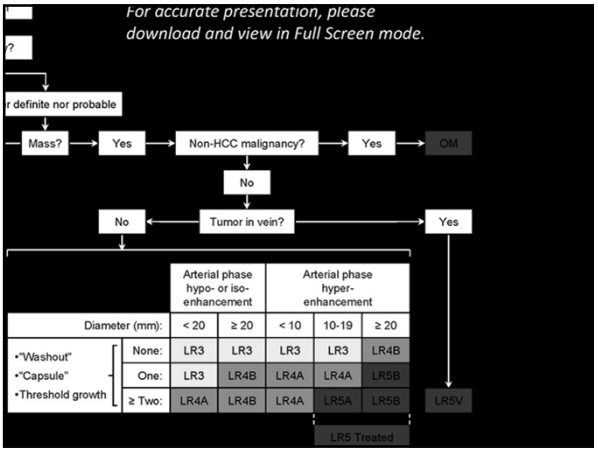
Blood supply to HCC predominantly Hepatic Artery
Characteristic findings on dynamic cross-sectional imaging highly reliable for DX in setting of high risk patient and increasing size
Meanwhile, biopsy needle-track spread of tumor in up to 5% and sensitivity is about 90% if lesion > 1 cm Mullhaupt B et al Is Tumor Biopsy Necessary? Liver Transplantation 2011 17:S14



Microspheres injected during transarterial therapy "lock in" chemotherapy.



For accurate presentation, please download and view in Full Screen mode.



Note this Paradigm shift…

- A liver mass in a cirrhotic patient is NOT an Oncology referral
  - Unless clearly metastatic
- A HCC in a cirrhotic patient can usually be diagnosed without biopsy
- A HCC in a cirrhotic patient must trigger consideration of OLT

What I tell patients re HCC

- No treatment: no 5 year survival
- Resection: up to 50% 5 year survival, but with recurrence rates as high as 70% at 5 years reviewed: S Didier et al Liver Transplantation 2011; 17:S6
- Loco-regional Rx – 45% 5 yr survival ibid
- OLT – 75% 5 year survival

OLT - Milan

- Landmark study Mazzaferro et al N Engl J Med 1996 Mar 14;334(11):693-9
- 48 patients with small unresectable hepatoma
- Eligibility for transplantation- one tumor < 5 cm or 3 nodules ≤ 3; no extrahepatic or vascular involvement
- 33 received pre op chemo- embolization
- Overall survival-75%
  - Pathologic review of explant:
    - 35 pts had tumors meeting inclusion criteria - survival 85%; recurrence-free survival 92%
    - 13 pts had tumors beyond inclusion criteria - survival 50%; recurrence-free survival 59%

HCC – Ultimate Treatment

- The proportion of patients with HCC on waiting lists for liver transplantation has increased dramatically
  - >30% in France
  - 26% across Europe
  - 34% in the United States

Samuel D, Colombo M, El-Serag H, Liver Transplantation, 17:S6-13, 2011

HCC & OLT

- NM is UNOS region 5
- Nobody in the region transplants much below MELD 35
- 6 months AFTER listing the HCC OLT candidate is awarded MELD 22
- MELD "points" accrue 10% quarterly
- Hence UPON LISTING the HCC patient has 18 months or so till OLT

- Pitfalls:
- Obliterate "HCC" before OLT center affirms Dx
- Spend 6 months doing loco-regional Rx, treating Hep C, addressing other medical issues BEFORE OLT evaluation considered…

OLT Evaluation – requires a careful exam…

But FIRST you have to recognize the potential candidate:

1) Cirrhotic with MELD – 15

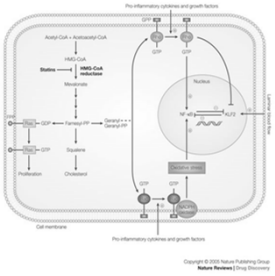
2) Liver Mass in setting of Chronic Liver Disease

Can we slow fibrogenesis…or carcinogenesis…?

CO Factors

- Alcohol Cessation
- Vigorous Exercise Kenji Tsuneda Yuko Kai et al. **"Impact of physical activity on nonalcoholic steatohepatitis in people with nonalcoholic simple fatty liver: A prospective cohort study"** Preventive Medicine Volume88, July 2016, Pages 237-240
- Weight Loss Tapper E, Lai M . **"Weight loss results in significant improvements in quality of life for patients with nonalcoholic fatty liver disease: A prospective cohort study."** Hepatology. 2016 Apr;63(4):1184-9. doi: 10.1002/hep.28416. Epub 2016 Feb 22.
- Are there Medicinals?
- (Protect them from the Liver Diseases they do NOT have – esp Hep A Vaccine)

Statin: Mechanism of Action



- Suppression of mevalonate pathway ➔ depletion of isoprenoids (role in cell cycle progression, cell signaling, and membrane integrity)

Statins…

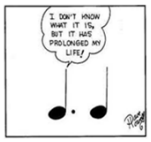
- Downregulate expression of profibrotic cytokines including tgf-beta and pdgf
- Upregulate kruppel-like factor 2 resulting in vasodilation and improved microcirculation
- Inhibit hepatic myofibroblast fibrogenesis and replication of HCV

Despite Increased Statin Use…AERs have not increased

- FDA Adverse Event Reporting System (AERS) database : statin-associated serious liver injury ≤2 per one million patient-years
- Severe liver injury cases: 30 of the 75 cases (14 deaths, 7 liver transplantations, and 9 severe liver injury) were assessed as possibly or probably associated with statin therapy. Russo et al. Spectrum of statin hepatotoxicity: Experience of the drug-induced liver injury network. Hepatology 2014;60:679–686.
- Current expert opinion to check baseline liver enzymes
- Strong recommendation against monitoring post-statin liver tests Bader et al. Liver tests are irrelevant when prescribing statins. Lancet 2010; 376 (9756): 1882-1883.

Statins in Chronic Liver Dz

- Statin use may reduce the risk for cirrhosis development in HCV-infected patients in a dose-dependent manner. Yao-Hsu Yang Wen-Cheng Chen et al . **Statin use and the risk of cirrhosis development in patients with hepatitis C virus infection** Journal of Hepatology Volume 63, Issue 5, November 2015, Pages 1111–1117
- Statin use associated with 59% risk reduction in HCC Singh et al. Statins are associated with a reduced risk of hepatocellular cancer: A systematic review and meta-analysis. Gastroenterology 2013;144:323–33



Take Home Points

- Think of chronic liver disease patients in terms of the spectrum of Decompensation
- MELD twice a year –
- Why or Why Not a candidate for OLT?
- Screen for HCC and avoid Oncology