Screening and Surveillance for Hepatocellular Carcinoma (HCC)

Judith Feinberg, MD
Project ECHO
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Risk Factors for HCC

• Cirrhosis from any cause is the primary risk factor
• ~ 80% occur in pts with cirrhosis and risk increases with fibrosis stage
• Chronic HCV and HBV are most common risk factors for HCC
• In U.S., ~50-60% of persons with HCC have chronic HCV
• Pts with chronic HCV and cirrhosis have a 2-5% annual risk and a 7%-14% risk over 5 years of developing HCC
• Risk in pts with HCV increases with substantial alcohol intake
  • the risk increases in a linear fashion with daily alcohol intake greater than 60 g (approximately 6 cans of beer, shots of liquor, or glasses of wine)
• Overall incidence rate of HCC is approximately three times higher in males than females
Risk of HCC by Sex in U.S., 2001-2006
Age-Adjusted Rates of HCC in the U.S., 1992-2005
Prognosis

• Overall prognosis is poor

• Est. median survival 4.3-20 months, 5-year survival 10-15%

• Pts with HCC detected after symptom onset have an extremely poor prognosis, with an overall 5-year survival 0-10%

• Symptoms may include:
  • Abdominal pain
  • Anorexia
  • Early satiety
  • Weight loss
  • Obstructive jaundice
  • Fever
  • Watery diarrhea
  • Bone pain (from metastases)
Survival After HCC Diagnosis

- **Screening Group**
  - Diagnosis: 100%
  - 1-year: 65.9%
  - 2-year: 59.9%
  - 3-year: 52.6%
  - 4-year: 52.6%
  - 5-year: 46.4%

- **Control Group**
  - Diagnosis: 31.2%
  - 1-year: 7.2%
  - 2-year: 7.2%
  - 3-year: 0.0%
  - 4-year: 0.0%
  - 5-year: 0.0%
Definition of Screening and Surveillance

• By definition, screening a pt for HCC means the pt has no symptoms and the clinician does not have a reason to suspect HCC
• The pt undergoes testing in order to detect HCC early, before the development of symptoms
• Surveillance is the process of serial application of the screening test to detect the presence of HCC before it becomes clinically suspected or evident
• Rationale: regular screening of at-risk asymptomatic pts may detect tumors at an early stage when potentially curative treatment can be offered
Rationale for Early Detection of HCC

• Potentially curative therapies
  • Hepatic resection (typically for solitary mass <5 cm)
  • Liver transplantation
INDICATIONS FOR HCC SURVEILLANCE IN PATIENTS WITH HEPATITIS C

• Any pt with advanced fibrosis or cirrhosis (Metavir stage 3 or 4)
• No clear-cut recommendations for pts with unknown stage of liver fibrosis. In this situation, some experts have suggested use of non-invasive markers to identify patients with probable advanced fibrosis or cirrhosis.
• Although HCC risk decreases substantially in pts with cirrhosis who obtain a sustained virologic response (cure) with therapy, the risk is not eliminated, even if they have documented improvement in cirrhosis
• **Recommended Surveillance Interval for Screening**: the interval time for surveillance is based on tumor doubling time, which generally is considered to occur in 6 to 12 months. Expert guidelines recommend using a surveillance interval of 6 months.
SURVEILLANCE TESTING METHODS: Alpha Fetoprotein (AFP)

- Most widely used biomarker for HCC surveillance
- Sensitivity of only 47-64% and a specificity of 82-95% for detecting HCC among HCV-infected patients
  - Due to lack of uniform secretion of AFP by HCC tumors
  - AFP is often elevated above the upper limit of normal in pts with advanced liver disease but without HCC
- AFP can be useful for HCC DX if the level is extremely elevated, but this isn’t common
- AFP is no longer recommended as routine surveillance test
  - if there is uncertainty about an imaging study and a biopsy cannot be performed, then AFP might provide useful additional information.
Surveillance: Radiographic Imaging

**Hepatic Ultrasound**
- Sensitivity of 65-80% and specificity 87-94% for detecting HCC
- The order should indicate it is for HCC screening
- Interpretation of is operator-dependent
- Can be difficult in pts who are obese or have underlying cirrhosis, particularly those with nodular cirrhosis

**CT**
- No current evidence exists for routine use of CT for routine surveillance
- Use a 4-phase (unenhanced, arterial, venous, and delayed) dynamic contrast CT scan as a secondary test for DX in pts with liver nodule >1 cm on ultrasound
- Characteristic finding is arterial hypervascularity (uptake) in the lesion followed by venous or delayed phase washout
- Role of 4-phase CT scan is particularly important since many experts rely on CT or MRI findings to establish HCC DX, without the need for liver biopsy
Surveillance: Radiographic Imaging

• MRI
  • Similar to recommendations for CT, no current evidence for use of MRI as a routine surveillance test
  • Dynamic contrast-enhanced MRI is often recommended as a secondary test for pts with nodule >1 cm on ultrasound
• Current guidelines recommend surveillance for HCC in pts with chronic HCV and advanced fibrosis or cirrhosis (Metavir stage F3 or F4)

• Recommended surveillance test is hepatic ultrasound every 6 months-- based on retrospective data and one prospective trial that primarily involved pts with chronic hepatitis B

• Surveillance should continue after patients receive therapy for HCV, even if they achieve an SVR

• AFP not recommended for surveillance-- evolving data show poor sensitivity and specificity
AASLD/IDSA Algorithm for Nodule on Ultrasound
Summary

• Cirrhosis is the most important risk factor for HCC
• HCC now fastest growing cause of cancer-related death in the U.S., due to rise in high HCV prevalence and aging of pts with chronic HCV
• Poor prognosis with an est. median survival 4.3-20 months
• Potentially curative therapies for early stage HCC are hepatic resection or liver transplantation
• Primary goal of HCC surveillance: detect disease in an early stage to increase the chance of potentially curative therapy
• Guidelines recommend surveillance with abdominal ultrasound every 6 months for all pts with HCV and advanced fibrosis or cirrhosis (Metavir stage F3 or F4)
• In pts with F3 or F4, successful treatment of HCV lowers the HCC risk, but does not eliminate it, so surveillance should continue even after they achieve an SVR
• Prior guidelines recommended using AFP in addition to ultrasound for HCC screening, but data showing low specificity and sensitivity of AFP has led to the recommendation to use ultrasound alone