ACG International Webinar Series:
Hepatocellular Carcinoma:
Epidemiology, Diagnosis and Treatment
Hosted by Pakistan Society for the Study of Liver Diseases

Speaker:
Patricia D. Jones
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ACG Governor - Pakistan

American College of Gastroenterology
ACG International Webinar Series
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June
Hepatocellular Carcinoma – Hosted by Pakistan Society for the Study of Liver Diseases
Speaker: Patricia D. Jones, MD, MSPH
Moderator: Dr. Zaigham Abbas
Date: Saturday, June 5th at 12:00 pm EST

August
Clinical Pearls for the Management of Pregnancy in IBD
Speaker: Sunanda V. Kane, MD, MSPH, FACP
Moderator: Dr. Gillian Watermeyer, MD
Date: Tuesday, August 31st at 12:00 pm EST

Visit https://gi.org/education/international-virtual-grand-rounds/ to Register

Participating in the Webinar

All attendees will be muted and will remain in Listen Only Mode.

Type your questions here so that the moderator can see them. Not all questions will be answered but we will get to as many as possible.
Hepatocellular Carcinoma: Epidemiology, Diagnosis and Treatment

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Division of Digestive Health and Liver Diseases, Department of Medicine
Sylvester Comprehensive Cancer Center
University of Miami Miller School of Medicine

Financial Relationships/ Commercial Interests

- Advisory Committee for the Hepatitis B Foundation Liver Cancer Disparities Project
- Expert panel for the American Gastroenterological Association Pfizer and grant from Pfizer and Crohn's and Colitis Foundation of America grant to address health disparities in IBD vaccination rates
- NIH funding (1R01MD012565-03; MPI Singal/Yopp; Pilot Award to U54MD010722-05, MPI: Wilkins-Vanderbilt/Weiss-UM)
Objectives:

• Appreciate the changing epidemiology of HCC
• Explain the diagnostic algorithm for HCC
• Understand the approach to treatment for HCC

Chief Complaint: Abdominal Pain

• 42 year-old man was in his usual state of health until he developed fever.
  • He went to urgent care and was sent home.
• The fever persisted. He also had pain in the RLQ so he went to the ER.
  • US and CT without contrast revealed a liver mass that was 7 cm in size
• One month later, CT scan with contrast was done and patient was noted to have a 13 x 11 x 10 cm mass suspicious for neoplasm. The lesion demonstrated peripheral arterial enhancement with a central persistent avascular low-density scar or necrosis.

• Risk Factors:
  • Never had a blood transfusion, surgery or tattoos.
  • Denies using intravenous drugs or intranasal cocaine.
  • He has never been tested for viral hepatitis
Family History:

- His father died of liver cancer 14 years prior
  - Diagnosed when he was in his 70s.
- At one point, the patient was told to wear gloves when caring for his father. However, the rationale for this was never explained.
- He does recall receiving the hepatitis B vaccines before coming to the US.
- He has children, ages 9 and 13, who were born in the US. They are healthy with no hepatitis B.
- His wife was likely tested during pregnancy, but he is unsure of the results.

Physical Examination/Diagnostic Tests

- Well-appearing with normal vital signs
  - 171 lbs, Height 5'5", BMI 28.5
  - Examination was unremarkable

- **AFP 15.3**
- **GGT 385**
- **Hepatitis B surface antigen: Reactive**
- **Hepatitis C antibody Nonreactive**

- Patient was discussed in Tumor Board
- Patient was started on Tenofovir
Liver Biopsy

**Moderately Differentiated Hepatocellular Carcinoma**

By Wong, Chun-Ming; Zhang, Chris Zhiyi; Liu, Lili; Cai, Muyan; Pan, Yinghua; Fu, Jia; Cao, Yun; Yun, Jingping - [2012]
Low SIRT3 Expression Correlates with Poor Differentiation and Unfavorable Prognosis in Primary Hepatocellular Carcinoma
PLoS ONE 7 (12): e51703. DOI:10.1371/journal.pone.0051703. ISSN 1932-6203.
hits://commons.wikimedia.org/w/index.php?curid=97933579

Well Differentiated  
Moderately Differentiated  
Poorly Differentiated

**Epidemiology of HCC:**

- **Incidence:**
  - Global: 600,000 new cases yearly
  - US: 25,000-30,000 new cases yearly
- Rarely develops in patients under age 40
- Incidence peaks at age 70
- **Male predominance** with 2:1 to 4:1 male:female ratio.
  - Men develop HCC 5 years earlier
- Primary liver cancer is the 7th most frequently occurring cancer worldwide but the 2nd most common cause of cancer mortality

Global Trends in HCC Incidence:

Age Standardized Incidence of HCC in Pakistan is 7.6/100,000 persons for males and 2.8/100,000 persons for females.

Concerning Trends:

HCC is the fastest growing cause of cancer-related death in men in the US.
Risk Factors for Hepatocellular Carcinoma:

- Cirrhosis
- Hepatitis B
- Hepatitis C
- Nonalcoholic Fatty Liver Disease
- Alcohol-Related Liver Disease
- Aflatoxin
- Vinyl chloride
- Diabetes
- Obesity

Cirrhosis is the Strongest Risk Factor for HCC

- 85-95% of patients with HCC have cirrhosis.¹
- The risk of developing HCC ranges from 1-8% each year.²
- The 5-year cumulative risk for development of HCC in patients with cirrhosis ranges from 5-30% and depends on etiology of liver disease, region, ethnicity, and stage of cirrhosis.³
  - The highest risk of HCC is among patients with decompensated cirrhosis.

² Journal of Hepatology 2018 vol. 69 j 182–236
Hepatitis C Virus:

- HCV is the leading cause of HCC in Pakistan; approximately 60% of HCC is HCV related.
- Risk of HCC in patients with HCV is estimated at 15-20 times that of those who do not have HCV.
  - Risk of developing HCC is 1-3%/year after 30 years of infection, secondary to promoting fibrosis and cirrhosis.
- Risk Factors
  - Older age at time of infection
  - Male gender
  - Co-infection with HIV or HBV
  - Heavy alcohol use (>50 g/day)
  - Possibly diabetes and obesity.


Direct Acting Antivirals and HCC Risk

- After initial concern that the incidence of HCC following successful DAA therapy appears to be higher than that observed after IFN therapies, more recent and larger studies have demonstrated that successful DAA therapy is associated with a 71% reduction in HCC risk.
- Three prospective French multicenter cohorts of more than 6,000 patients treated with DAA, of which 660 had curative therapy for HCC: No increased risk of HCC recurrence after DAA treatment when compared to non-DAA-treated controls.
- A systematic review performed on a total of 41 studies (n = 13,875 patients) showed no evidence of increased HCC recurrence risk in patients who achieved DAA-induced SVR compared to IFN-based SVR.
- Very recently, a meta-analysis concluded that there is no evidence that HCC occurrence or recurrence is different between patients receiving DAA or IFN therapy, but its strength is limited because of the inclusion of significantly heterogeneous studies without adequate follow-up for detecting HCC.
- Another large retrospective cohort study of hepatitis C virus patients (n = 22,500) who were treated with DAA examining in the VA population demonstrated a reduction in the incidence of hepatocellular carcinoma in patients achieving a SVR.

AASLD Practice Guidelines, 2018
EASL Clinical Practice Guidelines, 2018
SVR (Cure of HCV) reduces HCC risk

Hepatitis B Virus:

- 85% of cases occur in developing countries—highest incidence of HCC is in HBV-endemic regions.
- Risk Factors:
  - Genotypes C and D
  - Longer duration of infection
  - Asian or African race
  - Family history of HCC
  - Co-infection with HCV, HIV or HDV
  - Higher levels of HBV replication
  - Aflatoxin exposure
- 10-30% of patients with HBV-related HCC do not have cirrhosis.
- Annual liver cancer probability among patients with chronic HBV is ~ 0.5%; HCC incidence in inactive HBV carriers without liver cirrhosis is <0.3%/ year.


Obesity and Cancer Risk:

- Prostate (>35): 1.34
- Non-Hodgkin's Lymphoma (>35): 1.49
- All Cancers (>40): 1.52
- All Other Cancers (>39): 1.68
- Kidney (>33): 1.70
- Multiple Myeloma (>53): 1.71
- Gall Bladder (>39): 1.78
- Colon and Rectum (>39): 1.94
- Esophagus (>39): 1.91
- Stomach (>33): 2.61
- Pancreas (>33):
- Liver (>39): 4.52

Relative risk of death (95% confidence interval)


Diabetes and Hepatocellular Carcinoma:

Figure 8. Diabetes and the risk of HCC. The study examined 173,463 patients with diabetes and 650,620 without diabetes. No patient had acute or chronic liver disease recorded before, during, or within 1 year of his or her index hospitalization. Reprinted with permission.

El-Serag HB, Rudolph KL. Gastroenterology. 2007;132(7):2557-76
Nonalcoholic Fatty Liver Disease

The prevalence of NAFLD has doubled over the past two decades and is approximately 30%.

20% of patients with NAFLD-related HCC did not have cirrhosis
- Retrospective cohort study of 296,707 NAFLD patients in the VA.
- The absolute risk of HCC in NAFLD is low 0.21/1000 person-years or 0.8% five-year and 1.7% ten-year cumulative HCC risk.
- The absolute risk is too low in non-cirrhotic patients to recommend HCC surveillance.
- Risk was highest among oldest Hispanics.

Aflatoxin

Aflatoxins are a family of toxins produced by certain fungi that are found on agricultural crops such as maize (corn), peanuts, cottonseed, and tree nuts.
- The main fungi that produce aflatoxins are Aspergillus flavus and Aspergillus parasiticus, which are abundant in warm and humid regions of the world.
- Aflatoxin B1, G1 and M1 (encountered in animal products, such as milk)
Fewer than 10% of persons are diagnosed with HCC by screening in Pakistan.

https://doi.org/10.1155/2016/5942306
Improved Survival with Screening:

**Table 1.** Maximum tumor size at the time of initial detection in patients with HCC assorted by year of diagnosis

<table>
<thead>
<tr>
<th>Year</th>
<th>Mean maximum tumor size (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤ 2.0</td>
</tr>
<tr>
<td>1978-1980</td>
<td>1.3%</td>
</tr>
<tr>
<td>1981-1985</td>
<td>5.3%</td>
</tr>
<tr>
<td>1986-1990</td>
<td>14.5%</td>
</tr>
<tr>
<td>1991-1995</td>
<td>20.8%</td>
</tr>
<tr>
<td>1996-2000</td>
<td>17.9%</td>
</tr>
<tr>
<td>2001-2005</td>
<td>31.2%</td>
</tr>
</tbody>
</table>

Percentages are shown of patients with HCC in each time period assorted by maximum tumor size at the time of diagnosis.

- Since 1967, the Liver Cancer Study Group of Japan has maintained a nationwide prospective registry of all patients with HCC.
- Since the 1990s, Japan has implemented strategies educating physicians and patients about the risk or HCC.
- All patients are eligible for government supported screening.

Radiologic Screening Tools:

- **Ultrasound**
  - Sensitivity 0.73 (CI 0.46-0.90), Specificity 0.91 (CI 0.86-0.96)
  - May appear as echogenic, hypoechoic or a target lesion.
  - Operator-dependent and limited by obesity, steatosis, ascites, and nodularity
- **CT**
  - Sensitivity 0.83 (CI 0.75-0.89), Specificity 0.91 (CI 0.86-0.96)
  - Limited use in patients with CKD
- **MRI**
  - Sensitivity 0.86 (CI 0.79-0.91), Specificity 0.89 (CI 0.83-0.93)
  - MRI with low-dose gadolinium is safe

**Across modalities, sensitivity increases as tumor size increases.**

Neither CT nor MRI are **cost-effective** for surveillance and have increased risk of false-positives

Sheffer KM et al. Liver Transpl. 2015; Epub 2015/03/20
Serologic Screening Tools:

- **AFP:**
  - At cutoff of 20 ng/mL, AFP has sensitivity of approximately 60%.
  - Combined with US, AFP may detect 6-8% of cases not diagnosed by US alone.

- **AFP-L3:** ratio of glycosylated AFP (L3 fraction) to total AFP
  - Highly specific marker-sensitivity is 56%, specificity of >95%.
  - May have a 9-12 months lead-time in recognition of early HCC.

- **Des gamma carboxy prothrombin (DCP)/Prothrombin induced by vitamin K absence II (PIVKA II):**
  - Increases in patients with HCC and also patients on warfarin
  - Increases with tumor size and vascular invasion

- **When used in combination in a cohort of patients with low AFP, AFP-L3 (cutoff 5%) and PIVKA-II (cutoff 40 AU/L), sensitivity was 92.1% and specificity was 79.7%**

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AASLD Surveillance/Diagnostic Algorithm

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

AASLD Surveillance Algorithm

SURVEILLANCE

Surveillance ultrasound with or without AFP

Interpretation

Negative

Repeat US with or without AFP in 6 mo

Subthreshold (≥ 10 mm lesion but < 25 mm)

Repeat US with or without AFP in 3-6 mo

≥ 10 mm lesion or AFP ≥ 40 μg/L

Multiphase CT or MRI in select patients

Also endorsed by the Pakistan Society for the Study of Liver Disease (PSSLD)

AASLD Diagnostic Algorithm

DIAGNOSIS

Diagnostic imaging for HCC with multiphase CT or MRI

Interpretation

No observation detected

Negative No observation detected

LIRADS 1 No suspicion

LIRADS 2 Low suspicion

LIRADS 3 Moderate suspicion

LIRADS 4 High suspicion

LIRADS 5 Not interpretable

HCC confirmed

Recommended multidisciplinary discussion for tailored workup that may include biopsy (alcoholbased), or repeat or alternative diagnostic imaging in 3-6 mo

If biopsy

Pathology diagnosis

Pathology diagnosis

Footnotes

a. Multiphase CT or MRI in select patients

Some high-risk patients may undergo multiphase CT or MRI for HCC surveillance (depending on patient body habitus, visibility of liver at ultrasound, being on the transplant waiting list and other factors).

b. Noncategorizable

These are due to technical problems such as image artifact or severe degradation.
**Triple Phase CT**

Characteristic Radiologic Findings of HCC

*Back to our patient…..*

- Shrunken liver with a nodular contour
- 4 cm lesion noted with arterial hyperenhancement and washout.
- LI-RADS-5
- Non-occlusive thrombosis in main portal vein.

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**Accuracy of LI-RADS**

*Figure 2.* Percentage of HCC and overall malignancy for each LI-RADS category. The outer bubble margins correspond to 95% CIs for percentage of HCC (y-axis) and overall malignancy (x-axis). The central bubble dot corresponds to the pooled percentage of HCC and overall malignancy.

van der Poel CB, Lim CS et al. Gastroenterology. 2019; 156:976-986
TREATMENT OPTIONS

Barcelona Clinic Liver Cancer Staging: Treatment Recommendations

FIG. 3. Treatment recommendations according to BCLC Stage. Abbreviations: MWA, microwave ablation; BSC, best supportive care; 1L, first-line therapy; 2L, second-line therapy.

Risk Stratification for Liver Resection

<table>
<thead>
<tr>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IVa/IVb</th>
<th>V</th>
<th>VI</th>
<th>VII</th>
<th>VII</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caudate</td>
<td>Left</td>
<td>Right</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Liver Transplant

- Milan Criteria/BCLC Stage A
  - Single Nodule ≤5 cm in maximal diameter or 3 nodules each ≤ 3 cm
  - Overall and recurrence-free survival 85% and 92% respectively in persons meeting criteria. Overall and recurrence-free survival 50% and 59% for those exceeding Milan criteria.

- Patients exceeding criteria can be downstaged to within Milan Criteria and receive standard HCC MELD upgrade.
  - 1 lesion > 5 but ≤ 8 cm
  - 2-3 lesions each < 5 cm with total diameter of all lesions ≤ 8 cm
  - 4-5 lesions each < 3 cm with total diameter of all lesions ≤ 8 cm
  - AFP >1000 → < 500

- Exception Points are given to persons with HCC.

- Tumor thrombus is a contraindication
Ablative Therapies
EASL Clinical Practice Guidelines Slide Deck

- Percutaneous, Open or Laparoscopic
- Induces deep thermal injury in hepatic tissue leading to necrosis

Transarterial Embolization:

Bland embolization

Transarterial Chemoembolization (TACE):
- Emulsified chemotherapy vs. drug-eluting beads (Doxorubicin)
- Caution in patients with portal vein thrombosis

Transarterial Radioembolization (TARE)
- Iodine 131-labeled lipiodol
- Yttrium-90 labeled microspheres

Complications:
- Post-embolization syndrome (60-80%): RUQ pain, nausea, ileus, fatigue, fever, and transient elevations in AST, ALT, bilirubin
- Liver Failure (avoid if decompensated —bilirubin > 4 mg/dL)
- Biliary Complications
- Gastroduodenal ulceration
- Radiation hepatitis (1-2 months after RT)
External Beam Radiation:

• Useful in patients who have failed or refuse other modalities, have no extrahepatic disease and limited tumor burden.

• Contraindicated in patients with prior irradiation of the liver, including TARE.*

• Complications:
  • Radiation hepatitis (1-2 months after RT)
  • Liver Failure

https://www.cancer.gov/about-cancer/treatment/types/radiation-therapy/external-beam

Treatment Course (2016):

• Y-90 could not be performed due to shunt fraction of 30%
• TACE to right hepatic artery
• Portal vein embolization to attempt to grow left lobe for resection
  • Left lobe did not grow and tumor progressed to invade the portal vein
• Patient declined Sorafenib
• Inquired about clinical trial but did not qualify
• Transitioned to Hospice and died 10 months after diagnosis
Systemic Therapies

- **SHARP Trial**: Oral multi-kinase inhibitor of vascular endothelial growth factor (VEG-F) receptor, platelet-derived growth factor receptor and Raf kinases
- 400 mg po BID until no longer clinically benefitting or unacceptable toxicity.
- Included patients with performance status of 2 or less.
- Adverse Events: fatigue, hand-foot-skin reaction, anorexia, nausea, vomiting, diarrhea.
- Not an effective adjuvant drug following ablation or resection

**Regorafenib**

- **Oral multi-kinase inhibitor approved 4/27/2017 by FDA for treatment of HCC in patients treated with Sorafenib.**
- **RESORCE Trial:** International, multicenter, randomized, double-blind, placebo-controlled trial.
  - 573 patients with Child-Pugh A and BCLC Stage B or C HCC with disease progression on sorafenib.
- Significantly improved survival (HR=0.63, 95% CI: 0.50, 0.79, p<0.0001) with an estimated median overall survival for patients in the regorafenib arm of **10.6 months** and **7.8 months** for patients on placebo.
- The overall response rate, based on modified RECIST, was **11%** in the regorafenib arm and **4%** in the placebo arm.

**Lenvatinib**

- **Tyrosine kinase inhibitor of VEGF receptors 1–3, FGF receptors 1–4, PDGF receptor α, RET, and KIT**
- **REFLECT Trial:** Open label, phase 3 randomized, multicentered, non-inferiority trial
  - 954 patients (1:1) to sorafenib 400 mg BID or lenvatinib 8-12mg/day
  - Patients were BCLC B or C and Child Pugh A with ECOG 0/1
- Median overall survival was **13.6 months** for lenvatinib and **12.3 months** for sorafenib. There was no significant difference.
- **99%** of patients in both arms had adverse events; the rates of hand-skin-foot reaction was lower in those on lenvatinib while the rate of hypertension was lower in those on sorafenib.
**Cabozantinib**

- Tyrosine kinase inhibitor of vascular endothelial growth factor receptors 1, 2, and 3, MET, and AXL

**CELESTIAL** trial:
- Eligible patients had received previous treatment with sorafenib and disease progression after at least one systemic treatment.
- Median duration of receipt of the trial drug or placebo was 3.8 months in the cabozantinib group and 2.0 months in the placebo group.
- Side effects experienced in 99% of cabozantinib patients and 92% of those on placebo.
  - 46% of cabozantinib had hand-skin-foot reaction compared to 5% on placebo.
  - 29% of cabozantinib had hypertension compared to 6% on placebo

Abou-Alfa GK et al. NEJM 2018; 379: 54-63.

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**Mechanism of Immunotherapy**

PD-L1 binds to PD-1 and inhibits T cell killing of tumor cell

PD-L1

Antigen

PD-1

T cell receptor

T cell

Tumor cell

Blocking PD-L1 or PD-1 allows T cell killing of tumor cell

PD-L1

Anti-PD-L1

Anti-PD-1

T cell

Tumor cell death

Nivolumab

- **CheckMate 040**: Phase 1/2, open-label, non-comparative, dose escalation and expansion trial treated 262 patients. FDA Approved 9/22/2017.

- Nivolumab is a fully human IgG4 monoclonal antibody that disrupts PD-1 immune checkpoint signaling and thereby restores the antitumor activity.

- The objective response rate was 20% (95% CI 15–26) in patients treated with nivolumab 3 mg/kg in the dose-expansion phase and 15% (95% CI 6–28) in the dose-escalation phase. Three patients had a complete response.

- Three patients had treatment-related serious adverse events: pemphigoid, adrenal insufficiency, liver disorder.

Pembrolizumab

- **KEYNOTE-224**: Multi-centered open-label, phase 2 trial in 104 patients with pathologically confirmed HCC previously been treated with sorafenib. FDA-approved on 11/9/2018.

- Monoclonal antibody against PD-1
  - 200 mg IV q 3 weeks for up to 35 cycles

- **Response rates**:
  - One (1%) complete response
  - 17 (16%) partial responses
  - 46 (44%) patients had stable disease
  - 34 (33%) had progressive disease
  - Six (6%) were not assessable

- Treatment-related adverse events occurred in 76 patients (73%) and were serious in 16 (15%) patients.

- **KEYNOTE-240** was a randomized, double-blind phase 3 trial, (n = 413), comparing Pembrolizumab to best supportive care did not reach endpoints (OS & PFS)
  - Median overall survival was 13.9 months with Pembrolizumab vs. 10.6 months with placebo, p 0.02

**Ramucirumab**

- **REACH**: Randomized, double blind, multicentered phase 3 trial of 565 patients with advanced HCC following first-line therapy with Sorafenib.
- IgG1 monoclonal antibody and VEGF receptor-2 antagonist
- Median overall survival was 9.2 months in the Ramucirumab group and 7.6 months in the placebo group. Hazard ratio was 0.87, 95% Confidence interval of 0.72-1.05; p 0.14, therefore no significant survival differences.
- However, there was a significant survival benefit with Ramucirumab in patients with AFP >400
  - **REACH-2**: Median overall survival of 8.5 months in the Ramucirumab group vs 7.3 months in the placebo group. HR 0.71 (95% CI 0.53-0.95; p 0.02)
- FDA-approved on 5/10/2019 for patients who received Sorafenib in the first line and who have AFP > 400 ng/mL.

**Atezolizumab/Bevacizumab**

- **IMbrave150**: Global, multicentered, open label phase 3 randomized trial
  - 336 patients in atezolizumab-bevacizumab arm
  - 165 patients in sorafenib arm
  - Atezolizumab selectively targets PD-L1
  - Bevacizumab is a monoclonal antibody that targets VEGF
  - Eighteen patients (5.5%) in the atezolizumab/bevacizumab arm had complete response compared to zero patients in the sorafenib arm.
  - Atezolizumab/Bevacizumab was associated with higher quality of life.
  - There was no significant difference in Grade 3-5 adverse events.
  - 49.5% of Atezo/Bev arm had dose interruption of treatment, compared to 41% of Sorafenib
- FDA approved on 5/29/2020
Survival

- Prognosis is poor.
  - Mortality to Incidence ratio is 0.95
- Five—year survival ranges from 10-18%
  - Depends on stage at diagnosis.

Take Home Points

- All patients with cirrhosis should be screened for HCC every six months.
- Ultrasound ± AFP is the recommended screening modality.
  - Some patient characteristics may require cross-sectional imaging.
- A team-based multidisciplinary approach to HCC management is standard of care.
  - Treatment must be individualized based on tumor burden, performance status and liver function.
- The treatment landscape has changed dramatically in the last two years and there are new treatments on the horizon.
References:


References:

References:


* Co-first author

References:


References:


