Hepatocellular Carcinoma

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INITIAL EVALUATION

- History and physical
- CBC with differential, liver function test (LFTs), creatinine, electrolytes, PT/INR, lipoprotein profile, hemoglobin A1C, alpha-fetoprotein (AFP)
- Viral serologies if not known (HBV core and surface antibody (Ab); HBV DNA titer if HBV core and antigen positive; HCV Ab or RNA if Ab positive; HIV serology if HCV Ab positive or HBV core Ab positive)
- Diagnostic imaging:
  - Triple phase CT (preferred) or MRI abdomen and pelvis
  - CT chest with contrast
- Consider consult if indicated:
  - Hepatology for chronic liver disease or HBV treatment
  - Infectious Diseases for HCV or HIV treatment
- Lifestyle risk assessment

TREATMENT

Liver-only disease

Resectable or transplantable

Yes

Surgery

No

See Page 2 for unresectable tumors

Metastatic disease

Solitary metastasis

Yes

Consider loco-regional therapies if primary tumor is resectable in select cases

Performance status 0-2, CLIP 0-3, and Child-Pugh A-B and bilirubin less than or equal to 3 mg/dL

No

Performance status greater than 2, CLIP 4-6, or Child-Pugh C or bilirubin greater than 3 mg/dL

Further treatment based on primary liver lesions

Systemic treatment

Best supportive care

SURVEILLANCE

- History and physical
- CBC with differential, LFTs, electrolytes, PT/INR, AFP
- Triple phase CT (preferred) or MRI abdomen and CT chest every 4 months for 2 years, then every 6 months for 3 years, then annually

1 See Physical Activity, Nutrition, and Tobacco Cessation algorithms; ongoing reassessment of lifestyle risks should be a part of routine clinical practice
2 Consider MD Anderson approved hepatocellular biomarkers
3 Resection is considered for single or multiple tumors (up to 3 tumors). Macroscopic vascular invasion or portal hypertension is not a contraindication to resection.
4 Major and minor resection based on:
   - Minor resection: Child-Pugh A, normal liver function tests (bilirubin less than or equal 1.0 mg/dL), absence of ascites, and platelet count greater than 100 K/microliter
   - Major resection: Same as minor resection plus either absence of portal hypertension or portal vein embolization (PVE) for a small future liver remnant
5 Milan criteria (criteria for eligibility for liver transplantation for patients with hepatocellular carcinoma and cirrhosis) the presence of a tumor 5 cm or less in diameter in patients with single hepatocellular carcinomas; or no more than three tumor nodules, each 3 cm or less in diameter; in patients with multiple tumors, and without macrovascular invasion per imaging studies
6 Loco-regional therapies including ablation, transarterial arterial chemoembolization (TACE), and transarterial radioembolization (TARE) can be offered for bridging/down staging liver transplant patients
7 Child-Pugh
8 See Appendix A for Eastern Cooperative Oncology Group (ECOG) performance status
9 See Appendix B for determination of Cancer of Liver Italian Program (CLIP) Investigators score
10 See Appendix C for Child-Pugh scores
11 See Appendix D for Systemic Therapy options
12 Treatment may be considered in select cases with bilirubin 2-3 mg/dL

Note: Consider Clinical Trials as treatment options for eligible patients.
Hepatocellular Carcinoma

Note: Consider Clinical Trials as treatment options for eligible patients.

CLINICAL PRESENTATION FOR NOT CONSIDERED FOR RESECTION OR TRANSPLANTATION TUMORS

- Performance status\(^1\) 0-2, CLIP\(^2\) 0-3, Child-Pugh\(^3\) A-B and bilirubin less than or equal to 3 mg/dL

  - Early/Intermediate disease
    - Well defined lesions?
      - Yes
        - Advanced disease (extensive vascular involvement, infiltrative morphology, ill-defined disease, high tumor burden >50%, or metastatic disease)
      - No
        - Up to 3 lesions that are less than or equal to 3 cm in size
        - Single lesion greater than 3 cm up to 6.5 cm
        - Multiple lesions (up to 3-4)
        - Overall tumor burden < 25%
        - Single lesion 25-50% tumor burden
        - Single lesion > 6.5 cm with or without satellite nodules
        - Multiple lesions greater than 4
        - Any tumor burden above with portal vein or hepatic vein tumor thrombus

  - Intermediate disease
    - Well defined lesions?
      - Yes
        - Advanced disease (extensive vascular involvement, infiltrative morphology, ill-defined disease, high tumor burden >50%, or metastatic disease)
      - No
        - Up to 3 lesions that are less than or equal to 3 cm in size
        - Single lesion greater than 3 cm up to 6.5 cm
        - Multiple lesions (up to 3-4)
        - Overall tumor burden < 25%
        - Single lesion 25-50% tumor burden
        - Single lesion > 6.5 cm with or without satellite nodules
        - Multiple lesions greater than 4
        - Any tumor burden above with portal vein or hepatic vein tumor thrombus

TREATMENT\(^4\)

- Ablation (preferred or clinical trial if appropriate)
- Other alternative loco-regional therapies
  - TACE
  - Combination of ablation and TACE when clinically appropriate
  - Radioembolization

- TACE (preferred or clinical trial if appropriate)
- Other alternative loco-regional therapies
  - Combination of TACE and ablation when appropriate
  - Radioembolization
  - Neoadjuvant PIAF when clinically appropriate

- Radioembolization or radiation therapy (preferred or clinical trial if appropriate)
- Other alternative loco-regional therapies
  - Neoadjuvant PIAF when clinically appropriate
  - TACE

- Radioembolization with or without systemic therapy (preferred or clinical trial if appropriate)
- Other alternative loco-regional therapies
  - Radiation therapy
  - Neoadjuvant PIAF when histology is confirmed to be fibrolamellar HCC
  - TACE in select cases where lesions grouping allows for selective TACE

- Systemic therapy with or without radioembolization or radiation therapy (preferred or clinical trial if appropriate)
- Other alternative loco-regional therapies
  - TACE in select cases where lesions grouping allows for selective TACE

Best supportive care

RE-STAGING WORKUP

- History and physical
- CBC with differential, LFTs, AFP, electrolytes
- Triple phase CT abdomen and CT chest every 2 months until stable disease, then every 3 months for 2 years, then every 6 months for 3 years, then annually
- Multiphasic MRI abdomen with extracellular contrast agent if steatosis present
- Consider resection, transplantation or another loco-regional therapy

\(^1\) Based on patient’s clinical status, co-morbidities, tumor characteristics, and multi-disciplinary discussions
\(^2\) See Appendix B for CLIP Investigators score
\(^3\) See Appendix C for Child-Pugh scores
\(^4\) See Appendix A for ECOG performance status

HCC = Hepatocellular Carcinoma
PIAF = cisplatin, interferon-alfa, 5-fluorouracil and doxorubicin
TACE = transcatheter arterial chemoembolization
APPENDIX A: Eastern Cooperative Oncology Group (ECOG) Performance Status Criteria

<table>
<thead>
<tr>
<th>Grade</th>
<th>Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction (Karnofsky 90-100)</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, <em>i.e.</em>, light housework, office work (Karnofsky 70-80)</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60)</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair more than 50% of waking hours (Karnofsky 30-40)</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair (Karnofsky 10-20)</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>

APPENDIX B: Cancer of Liver Italian Program (CLIP) Scoring System

<table>
<thead>
<tr>
<th>Variables</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child-Pugh Class</td>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>Tumor morphology</td>
<td>Uninodular and extension less than or equal to 50%</td>
<td>Multinodular and extension less than or equal to 50%</td>
<td>Massive or greater than 50%</td>
</tr>
<tr>
<td>AFP</td>
<td>Less than 400 ng/dL</td>
<td>Greater than or equal to 400 ng/dL</td>
<td></td>
</tr>
<tr>
<td>Portal vein thrombosis</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

AFP = alpha fetoprotein
APPENDIX C: Child-Pugh Scoring System

<table>
<thead>
<tr>
<th>Chemical and Biochemical Parameters</th>
<th>Scores (Points) for Increasing Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Encephalopathy*</td>
<td>None</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
</tr>
<tr>
<td>Albumin</td>
<td>Greater than 3.5 g/dL</td>
</tr>
<tr>
<td>Prothrombin time prolonged</td>
<td>1 – 4 seconds</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>1 – 2 mg/dL</td>
</tr>
<tr>
<td>For primary biliary cirrhosis</td>
<td>1 – 4 mg/dL</td>
</tr>
</tbody>
</table>

*Grades for encephalopathy:
Grade I: Altered mood/confusion
Grade II: Inappropriate behavior, impending stupor, somnolence
Grade III: Markedly confused, stuporous but arousable
Grade IV: Comatose/unresponsive

Score interpretation:
Class A = 5 to 6 points
Class B = 7 to 9 points
Class C = 10 to 15 points
**APPENDIX D: Systemic Therapy**

### Frontline systemic therapy for patients with advanced HCC and Child-Pugh A

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose and Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab plus bevacizumab</td>
<td>Atezolizumab 1200 mg IV and bevacizumab 15 mg/kg IV every 3 weeks</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>12 mg PO daily for patients ≥ 60 kg and 8 mg for patients &lt; 60 kg</td>
</tr>
<tr>
<td>Sorafenib (Child-Pugh A or B)</td>
<td>400 mg PO twice daily</td>
</tr>
<tr>
<td>Nivolumab (if patients ineligible or intolerant to other frontline medications, Child-Pugh A or B)</td>
<td>240 mg IV every 2 weeks or 480 mg IV every 4 weeks</td>
</tr>
</tbody>
</table>

### Subsequent line systemic therapy for patients with advanced HCC and Child-Pugh A

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose and Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabozantinib (Cabometyx®)</td>
<td>60 mg PO daily</td>
</tr>
<tr>
<td>Nivolumab (Child-Pugh A or B)</td>
<td>240 mg IV every 2 weeks or 480 mg IV every 4 weeks</td>
</tr>
<tr>
<td>Ipilimumab plus nivolumab</td>
<td>Ipilimumab 3 mg/kg IV and nivolumab 1 mg/kg IV every 3 weeks for 4 doses, followed by single-agent nivolumab 240 mg every 2 weeks or 480 mg every 4 weeks</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>200 mg IV every 3 weeks or 400 mg IV every 6 weeks</td>
</tr>
<tr>
<td>Ramucirumab (if AFP ≥ 400)</td>
<td>8 mg/kg IV every 2 weeks</td>
</tr>
<tr>
<td>Regorafenib</td>
<td>160 mg once a day for 21 days on and 7 days off of each 28-day cycle</td>
</tr>
<tr>
<td>Sorafenib (Child-Pugh A or B)</td>
<td>400 mg PO twice daily</td>
</tr>
</tbody>
</table>

### Dose and Schedule

- **Atezolizumab**: 1200 mg IV and bevacizumab 15 mg/kg IV every 3 weeks
- **Lenvatinib**: 12 mg PO daily for patients ≥ 60 kg and 8 mg for patients < 60 kg
- **Sorafenib**: 400 mg PO twice daily
- **Nivolumab**: 240 mg IV every 2 weeks or 480 mg IV every 4 weeks
- **Ipilimumab plus nivolumab**: Ipilimumab 3 mg/kg IV and nivolumab 1 mg/kg IV every 3 weeks for 4 doses, followed by single-agent nivolumab 240 mg every 2 weeks or 480 mg every 4 weeks
- **Pembrolizumab**: 200 mg IV every 3 weeks or 400 mg IV every 6 weeks
- **Ramucirumab**: 8 mg/kg IV every 2 weeks
- **Regorafenib**: 160 mg once a day for 21 days on and 7 days off of each 28-day cycle
- **Sorafenib**: 400 mg PO twice daily

**AFP = alpha fetoprotein**

1. MD Anderson will abide by FDA label for starting doses for eligible patients. In some case scenarios, where liver functions are borderline, our clinical discretion leads to starting with variables doses and schedules which is personalized in this setting.
**Ablation**


**Chemoembolization**


**Child-Pugh score**


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**SUGGESTED READINGS**

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SUGGESTED READINGS

CLIP score

Neoadjuvant Chemotherapy

Radiofrequency Ablation (RFA)

Radiation therapy

Continued on Next Page
Radioembolization

Surgery

Continued on Next Page
Hepatocellular Carcinoma

Surgery - continued


Systemic Therapy


SUGGESTED READINGS - continued
SUGGESTED READINGS - continued


DEVELOPMENT CREDITS

This practice guideline is based on majority expert opinion of the Gastrointestinal Center Faculty at the University of Texas MD Anderson Cancer Center. It was developed using a multidisciplinary approach that included input from the following:

Thomas Aloia, MD (Surgical Oncology)
Olga N. Fleckenstein
Hyunseon Christine Kang, MD, PhD (Diagnostic Radiology – Body Imaging)
Ahmed O. Kaseb, MD (GI Medical Oncology)
Harmeet Kaur, MD (Diagnostic Radiology – Body Imaging)
Eugene Koay, MD, PhD (Radiation Oncology Department)
Joshua Kuban, MD (Interventional Radiology)
Sunyoung Lee, MD, PhD (GI Medical Oncology)
Evelyne Loyer, MD (Diagnostic Radiology – Body Imaging)
Armeen Mahvash, MD (Interventional Radiology)
Ethan Miller, MD (Hepatology)
Bruno Odisio, MD (Interventional Radiology)
Jean-Nicolas Vauthey, MD (Surgical Oncology)
Milena Zhang, PharmD

†Core Development Team Lead
* Clinical Effectiveness Development Team