Hepatocellular Carcinoma

INITIAL EVALUATION

- History and physical
- CBC with differential, liver function test (LFTs), creatinine, electrolytes, PT/INR, lipid 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 CT chest
- 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\(^2\) or transplantable\(^3,5,9\)

Yes

Surgery\(^7\)

No

See Page 2 for unresectable tumors

Solitary metastasis\(^2,9\)

Performance status\(^6\) 0-2, CLIP\(^7\) 0-3, and Child-Pugh\(^8\) A-B and bilirubin \(\leq 3\) mg/dL

Yes

Further treatment based on primary liver lesions

No

Performance status\(^6\) > 2, CLIP\(^7\), 4-6, or Child-Pugh\(^8\) C or bilirubin > 3 mg/dL\(^9\)

Systemic treatment\(^9\)

Metastatic disease

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

\(^1\) 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. 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 > 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
\(^4\) 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
\(^5\) Loco-regional therapies including ablation, transcatheter arterial chemoembolization (TACE), and transarterial radioembolization (TARE) can be offered for bridging/down staging liver transplant patients
\(^6\) See Appendix A for Eastern Cooperative Oncology Group (ECOG) performance status
\(^7\) See Appendix B for determination of Cancer of Liver Italian Program (CLIP) Investigators score
\(^8\) See Appendix C for Child-Pugh scores
\(^9\) See Appendix D for Systemic Therapy options
\(^10\) Treatment may be considered in select cases with bilirubin 2-3 mg/dL
\(^11\) Goal Concordant Care (GCC) should be initiated by the Primary Oncologist. If Primary Oncologist is unavailable, Primary Team/Attending Physician to initiate GCC discussion and notify Primary Oncologist. Patients or if clinically indicated the SDM should be informed of therapeutic and/or palliative options. GCC discussion should be consistent, timely, and re-evaluated as clinically indicated. The Advance Care Planning (ACP) note should be used to document GCC discussion. Refer to GCC home page (for internal use only).

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

**CLINICAL PRESENTATION FOR NOT CONSIDERED FOR RESECTION OR TRANSPLANTATION TUMORS**

- **Performance status** 1-2, CLIP 0-3, Child-Pugh A-B and bilirubin ≤ 3 mg/dL
- **Well defined lesions?** Yes
- **Early/Intermediate disease**
  - 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
- **Advanced disease (extensive vascular involvement, infiltrative morphology, ill-defined disease, high tumor burden >50%, or metastatic disease)**
  - Multiple lesions greater than 4
  - Single lesion 25-50% tumor burden
  - Single lesion > 6.5 cm with or without satellite nodules
  - Any tumor burden above with portal vein or hepatic vein tumor thrombus

**TREATMENT**

- **Up to 3 lesions that are ≤ 3 cm in size**
  - Ablation (preferred or clinical trial if appropriate)
  - Other alternative loco-regional therapies
    - TACE/Radioembolization
    - Combination of ablation and TACE when clinically appropriate
  - Neoadjuvant treatment when clinically appropriate

- **Single lesion greater than 3 cm up to 6.5 cm**
  - Radioembolization or radiation therapy (preferred or clinical trial if appropriate)
  - Other alternative loco-regional therapies
    - Neoadjuvant treatment when clinically appropriate
    - TACE
  - If cancer is deemed aggressive, systemic therapy options with loco-regional therapy are considered

- **Multiple lesions (up to 3-4)**
  - Radioembolization with or without systemic therapy (preferred or clinical trial if appropriate)
  - Other alternative loco-regional therapies
    - Radiation therapy
    - Neoadjuvant treatment when histology is confirmed to be fibrolamellar HCC
    - TACE in select cases where lesions grouping allows for selective TACE

- **Overall tumor burden < 25%**
  - 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

- **Single lesion 25-50% tumor burden**
  - Radioembolization or radiation therapy (preferred or clinical trial if appropriate)
  - Other alternative loco-regional therapies
    - Neoadjuvant treatment when clinically appropriate
    - TACE
  - If cancer is deemed aggressive, systemic therapy options with loco-regional therapy are considered

- **Single lesion > 6.5 cm with or without satellite nodules**
  - Radioembolization or radiation therapy (preferred or clinical trial if appropriate)
  - Other alternative loco-regional therapies
    - Neoadjuvant treatment when clinically appropriate
    - TACE
  - If cancer is deemed aggressive, systemic therapy options with loco-regional therapy are considered

- **Any tumor burden above with portal vein or hepatic vein tumor thrombus**
  - Systemictherapy 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

**STAGING**

- **Performance status** 1-2, CLIP 0-3, Child-Pugh A-B and bilirubin ≤ 3 mg/dL
- **Well defined lesions?** Yes
- **Advanced disease (extensive vascular involvement, infiltrative morphology, ill-defined disease, high tumor burden >50%, or metastatic disease)**
  - 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
  - Any tumor burden above with portal vein or hepatic vein tumor thrombus

**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**
  - Multifocal MRI abdomen with extracellular contrast agent if steatosis present
  - Consider resection, transplantation or another loco-regional therapy

**Best supportive care**

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1. Performance status: see Appendix A for ECOG performance status
2. CLIP score: see Appendix B for determination of Cancer of Liver Italian Program (CLIP) Investigators score
3. Child-Pugh score: see Appendix C for Child-Pugh scores
4. Systemic therapy: see Appendix D for Systemic Therapy options
5. Radioembolization or radiation therapy: see Appendix E for Radioembolization or radiation therapy options
6. Bilirubin levels: may be considered in select cases with bilirubin 2-3 mg/dL

Disclaimer: This algorithm has been developed for MD Anderson using a multidisciplinary approach considering circumstances particular to MD Anderson’s specific patient population, services and structure, and clinical information. This is not intended to replace the independent medical or professional judgment of physicians or other health care providers in the context of individual clinical circumstances to determine a patient's care. This algorithm should not be used to treat pregnant women.
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, i.e., 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

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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

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### 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 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 contraindicated 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>
| Tremelimumab plus durvalumab                  | ● Weight ≥ 30 kg: tremelimumab 300 mg IV as single dose at cycle 1/day 1 and durvalumab 1,500 mg IV, followed by durvalumab 1,500 mg IV monotherapy every 4 weeks  
  ● Weight < 30 kg: tremelimumab 4 mg/kg as a single dose at cycle 1/day 1 and durvalumab 20 mg/kg IV, followed by durvalumab 20 mg/kg IV monotherapy every 4 weeks |

#### 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>Lenvatinib (if not used previously)</td>
<td>12 mg PO daily for patients ≥ 60 kg and 8 mg for patients &lt; 60 kg</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>
</tbody>
</table>
| Nivolumab plus ipilimumab                     | ● Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg, administered every 3 weeks (4 doses), followed by nivolumab 240 mg every 2 weeks or  
  ● Nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks (alternative dosing option to improve tolerance) |
| Pembrolizumab                                  | 200 mg IV every 3 weeks or 400 mg IV every 6 weeks                    |
| Ramucirumab [if AFP (alfa fetoprotein) ≥ 400]  | 8 mg/kg IV every 2 weeks                                               |
| Regorafenib                                    | 160 mg PO once a day for 21 days on and 7 days off of each 28-day cycle |
| Sorafenib (Child-Pugh A or B)                  | 400 mg PO twice daily                                                  |

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.
2. Recommended to have baseline endoscopic evaluation and if indicated, esophageal varices management, within 6 months prior to starting treatment with atezolizumab and bevacizumab.
SUGGESTED READINGS

MD Anderson Institutional Policy #CLN1202 - Advance Care Planning Policy
Advance Care Planning (ACP) Conversation Workflow (ATT1925)

Ablation


Chemoembolization


Continued on Next Page

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Department of Clinical Effectiveness V8

Approved by Executive Committee of the Medical Staff 02/21/2023
SUGGESTED READINGS

Child-Pugh score

CLIP score

Radiofrequency Ablation (RFA)

Radiation therapy
Radioembolization


Surgery


SUGGESTED READINGS - continued

**Surgery - continued**


**Systemic Therapy**


SUGGESTED READINGS - continued

**Systemic Therapy – continued**


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:

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