Hepatocellular Carcinoma

Note: Consider Clinical Trials as treatment options for eligible patients

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 pelvis with and without contrast
  - 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[1]

TREATMENT

A Liver-only disease → Resectable[2,3] or transplantable[4,5]?
- Yes → Surgery[3] → SURVEILLANCE
- No → See Page 2 for unresectable tumors

B Metastatic disease → Solitary metastasis[2]?
- Yes → Consider loco-regional therapies if primary tumor is resectable in select cases → Further treatment based on primary liver lesions and liver function status (generally Child-Pugh A)
- No → Performance status[6] 0-2, CLIP[7] 0-3, and Child-Pugh[8] A-B and bilirubin ≤ 3 mg/dL → Further systemic treatment[9] based on liver function status
- No → Performance status[6] > 2, CLIP[7] 4-6, or Child-Pugh[8] C or bilirubin > 3 mg/dL → Best supportive care; Discuss Goal Concordant Care (GCC) with patient or if clinically indicated, with Patient Representative[10]

SURVEILLANCE

- History and physical
- CBC with differential, LFTs, electrolytes, PT/INR, AFP
- Triple phase CT (preferred) or MRI abdomen with and without contrast and CT chest with contrast every 4 months for 2 years, then every 6 months for 3 years, then annually

[1] See Physical Activity, Nutrition, Obesity Screening and Management, and Tobacco Cessation Treatment 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 ≤ 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 trans arterial 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 scores

[8] See Appendix C for Child-Pugh scores

[9] See Appendix D for Systemic Therapy for Patients with Advanced Hepatocellular Carcinoma options

[10] 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 Patient Representative 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).

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Hepatocellular Carcinoma

Note: Consider Clinical Trials as treatment options for eligible patients

CLINICAL PRESENTATION FOR UNRESECTABLE OR UNTRANSPLANTABLE TUMORS

Performance status[1] 0-2, CLIP[2] 0-3, Child-Pugh[3] A-B and bilirubin ≤ 3 mg/dL

Well defined lesions?

- Yes → Early/Intermediate disease
- No → See Page 3 for advanced disease

STAGING

Early/Intermediate disease

- Up to 3 lesions that are ≤ 3 cm in size
- Single lesion > 3 cm up to 6.5 cm; Multiple lesions (up to 3-4); Overall tumor burden < 25% of liver parenchyma
- Single lesion 25-50% of liver parenchyma; 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

PRIMARY 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 **or**
  - Combination of ablation and TACE when clinically appropriate **or**
  - Radiation therapy **or**
  - Neoadjuvant treatment when clinically appropriate

Single lesion > 3 cm up to 6.5 cm; Multiple lesions (up to 3-4); Overall tumor burden < 25% of liver parenchyma

- TACE/Radioembolization (preferred or clinical trial if appropriate)
- Other alternative loco-regional therapies
  - Combination of TACE and ablation when appropriate **or**
  - Radiation therapy **or**
  - Neoadjuvant treatment when clinically appropriate

Single lesion 25-50% of liver parenchyma; 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 **or** TACE
- If cancer is deemed aggressive, systemic therapy options with loco-regional therapy are considered

Multiple lesions (greater than 4)

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

Any tumor burden above with portal vein or hepatic vein tumor thrombus

- Systemic therapy **with or without** radioembolization[4] **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

RE-STAGING WORKUP

- History and physical
- CBC with differential, LFTs, AFP, electrolytes
- Triple phase CT abdomen with and without contrast and CT chest with contrast 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 (refer to Page 1: Box A if liver-only disease or Box B if metastatic disease)

HCC = Hepatocellular Carcinoma

[1] See Appendix A for ECOG performance status
[2] See Appendix B for determination of Cancer of Liver Italian Program (CLIP) Investigators scores
[3] See Appendix C for Child-Pugh scores
[4] Radioembolization for tumors with portal vein thrombosis is dependent on proper targeting based on planning angiography

Department of Clinical Effectiveness V9
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Hepatocellular Carcinoma

Note: Consider Clinical Trials as treatment options for eligible patients

CLINICAL PRESENTATION FOR UNRESECTABLE OR UNTRANSPLANTABLE TUMORS	PRIMARY TREATMENT	RE-STAGING WORKUP
Advanced disease (extensive vascular involvement, infiltrative morphology, ill-defined disease, high tumor burden > 50%, or metastatic disease)	• Systemic therapy[1] **or** • Apply treatment option pathways for early/intermediate disease if feasible **or** • Consider palliative radiotherapy for pain related to liver cancer	• History and physical • CBC with differential, LFTs, AFP, electrolytes • Triple phase CT abdomen with and without contrast and CT chest with contrast 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 (refer to Page 1: Box A if liver-only disease or Box B if metastatic disease)
Performance status[2] > 2, CLIP[3] 4-6, Child-Pugh[4] C or bilirubin > 3 mg/dL	Best supportive care	

[1] See Appendix D for Systemic Therapy for Patients with Advanced Hepatocellular Carcinoma
[2] See Appendix A for ECOG performance status
[3] See Appendix B for determination of Cancer of Liver Italian Program (CLIP) Investigators scores
[4] See Appendix C for Child-Pugh scores

Department of Clinical Effectiveness V9
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APPENDIX A: Eastern Cooperative Oncology Group (ECOG) Performance Status Criteria

Grade	Scale
0	Fully active, able to carry on all pre-disease performance without restriction (Karnofsky 90-100)
1	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)
2	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).
3	Capable of only limited self-care. Confined to bed or chair more than 50% of waking hours (Karnofsky 30-40).
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair (Karnofsky 10-20).
5	Dead

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

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

AFP = alpha fetoprotein

APPENDIX C: Child-Pugh Scoring System

Chemical and Biochemical Parameters	Scores (Points) for Increasing Abnormality		
	1	2	3
Encephalopathy*	None	Grade I - II	Grade III - IV
Ascites	None	Slight	Moderate
Albumin	Greater than 3.5 g/dL	2.8 – 3.5 g/dL	Less than 2.8 g/dL
Prothrombin time prolonged	Less than 4 seconds	4 – 6 seconds	Greater than 6 seconds
Bilirubin For primary biliary cirrhosis	Less than 2 mg/dL Less than 4 mg/dL	2 – 3 mg/dL 4 – 10 mg/dL	Greater than 3 mg/dL Greater than 10 mg/dL

*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 for Patients with Advanced Hepatocellular Carcinoma[1]

Frontline Systemic Therapy[2]	Dose and Schedule
Atezolizumab plus bevacizumab[3]	Atezolizumab 1,200 mg IV and bevacizumab 15 mg/kg IV every 3 weeks
Durvalumab (for patients ineligible or contraindicated to other frontline medications, preferred ICI if used as monotherapy)	Weight ≥ 30 kg: 1,500 mg IV every 4 week
Lenvatinib	• Weight ≥ 60 kg: 12 mg PO daily • Weight < 60 kg: 8 mg PO daily
Nivolumab (if patients ineligible or contraindicated to other frontline medications, Child-Pugh A or B)	240 mg IV every 2 weeks or 480 mg IV every 4 weeks
Sorafenib (Child-Pugh A or B)	400 mg PO twice daily
Tremelimumab plus durvalumab	• Weight ≥ 30 kg: tremelimumab 300 mg IV and durvalumab 1,500 mg IV on Day 1 of Cycle 1, followed by durvalumab 1,500 mg IV monotherapy every 4 weeks • Weight < 30 kg: tremelimumab 4 mg/kg and durvalumab 20 mg/kg IV on Day 1 of Cycle 1, followed by durvalumab 20 mg/kg IV monotherapy every 4 weeks

ICI = Immune Checkpoint Inhibitor

[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] Treatment options for patients with advanced hepatocellular carcinoma and Child Pugh A (unless otherwise specified)

[3] Recommended to have baseline endoscopic evaluation and if indicated, esophageal varices management, within 6 months prior to starting treatment with atezolizumab and bevacizumab

Continued on next page

APPENDIX D: Systemic Therapy for Patients with Advanced Hepatocellular Carcinoma[1] - continued

Subsequent Line Systemic Therapy[2]	Dose and Schedule
Cabozantinib (Cabometyx®)[3]	60 mg PO daily
Lenvatinib (if not used previously)	• Weight ≥ 60 kg: 12 mg PO daily • Weight < 60 kg: 8 mg PO daily
Nivolumab (Child-Pugh A or B)	240 mg IV every 2 weeks or 480 mg IV every 4 weeks
Nivolumab plus ipilimumab	• Nivolumab 1 mg/kg and ipilimumab 3 mg/kg, administered every 3 weeks for 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 ≥ 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; if not used previously)	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] Treatment options for patients with advanced hepatocellular carcinoma and Child Pugh A (unless otherwise specified)
[3] Not on MD Anderson formulary

SUGGESTED READINGS

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

Ablation

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SUGGESTED READINGS - continued

Systemic Therapy – continued

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