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
  - 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

Liver-only disease

Resectable[2,3] or transplantable[4,5]?

- Yes → Surgery[3]
- No → See Page 2 for unresectable tumors

Metastatic disease

Solitary metastasis[2]?

- Yes → Consider loco-regional therapies if primary tumor is resectable in select cases
- No → Performance status[6] 0-2, CLIP[7] 0-3, and Child-Pugh[8] A-B and bilirubin less than or equal to 3 mg/dL → Systemic treatment[9]
- No → Performance status[6] greater than 2, CLIP[7] 4-6, or Child-Pugh[8] C or bilirubin greater than 3 mg/dL[10] → 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

Further treatment based on primary liver lesions

[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 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

[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

Department of Clinical Effectiveness V7
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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

Well defined lesions?

- Yes → Early/ Intermediate disease
- No → Advanced disease (extensive vascular involvement, infiltrative morphology, ill-defined disease, high tumor burden >50%, or metastatic disease)

STAGING

- 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
  - Radiation therapy
  - Neoadjuvant PIAF when clinically appropriate

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

Apply treatment options pathways for early/intermediate disease but consider adding systemic therapy[5] as a stand alone option or in combination with local therapy if feasible

Performance status[1] greater than 2, CLIP[2] 4-6, Child-Pugh[3] C or bilirubin greater than 3 mg/dL[6] → 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

HCC= Hepatocellular Carcinoma
NED = no evidence of disease
PIAF = cisplatin, interferon-alfa, 5-fluorouracil and doxorubicin
TACE = transcatheter arterial chemoembolization

[1] See Appendix A for ECOG performance status
[2] See Appendix B for determination of Cancer of Liver Italian Program (CLIP) Investigators score
[3] See Appendix C for Child-Pugh scores
[4] Based on patient's clinical status, co-morbidities, tumor characteristics, and multi-disciplinary discussions
[5] See Appendix D for Systemic Therapy options
[6] Treatment may be considered in select cases with bilirubin 2-3 mg/dL

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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	1 – 4 seconds	4 – 6 seconds	Greater than 6 seconds
Bilirubin For primary biliary cirrhosis	1 – 2 mg/dL 1 – 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[1]

Frontline systemic therapy for patients with advanced HCC and Child-Pugh A	Dose and Schedule
Atezolizumab plus bevacizumab	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 (Child-Pugh A or B)	400 mg PO twice daily
Nivolumab (if patients ineligible or intolerant to other frontline medications, Child-Pugh A or B)	240 mg IV every 2 weeks or 480 mg IV every 4 weeks

Subsequent line systemic therapy for patients with advanced HCC and Child-Pugh A	Dose and Schedule
Cabozantinib (Cabometyx®)	60 mg PO daily
Nivolumab (Child-Pugh A or B)	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 (if AFP ≥ 400)	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 (Child-Pugh A or B)	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

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