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 → Further treatment based on primary liver lesions
- No →
  - Performance status[6] 0-2, CLIP[7] 0-3, and Child-Pugh[8] A-B and bilirubin ≤ 3 mg/dL → Systemic treatment[9]
  - Performance status[6] > 2, CLIP[7] 4-6, or Child-Pugh[8] C or bilirubin > 3 mg/dL[10] →
    - Best supportive care
    - Discuss Goal Concordant Care (GCC) with patient or if clinically indicated, with Surrogate Decision-Maker (SDM)[11]

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. 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).

Department of Clinical Effectiveness V8
Approved by Executive Committee of the Medical Staff 02/21/2023

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 ≤ 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 ≤ 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/Radioembolization
  - Combination of ablation and TACE when clinically appropriate
  - Radiation therapy
  - Neoadjuvant treatment when clinically appropriate

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

- 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

- 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

- 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 > 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
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

Department of Clinical Effectiveness V8
Approved by Executive Committee of the Medical Staff 02/21/2023

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[2]	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 contraindicated to other frontline medications, Child-Pugh A or B)	240 mg IV every 2 weeks or 480 mg IV every 4 weeks
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	Dose and Schedule
Cabozantinib (Cabometyx®)	60 mg PO daily
Lenvatinib (if not used previously)	12 mg PO daily for patients ≥ 60 kg and 8 mg for patients < 60 kg
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 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

Cucchetti, A., Piscaglia, F., Cescon, M., Colecchia, A., Ercolani, G., Bolondi, L., & Pinna, A. D. (2013). Cost-effectiveness of hepatic resection versus percutaneous radiofrequency ablation for early hepatocellular carcinoma. *Journal of Hepatology, 59*(2), 300-307. doi:10.1016/j.jhep.2013.04.009

Feng, K., Yan, J., Li, X., Xia, F., Ma, K., Wang, S., … Dong, J. (2012). A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. *Journal of Hepatology, 57*(4), 794-802. doi:10.1016/j.jhep.2012.05.007

Shiina, S., Tateishi, R., Arano, T., Uchino, K., Enooku, K., Nakagawa, H., … Kazuhiko Koike. (2012). Radiofrequency ablation for hepatocellular carcinoma: 10-year outcome and prognostic factors. *The American Journal of Gastroenterology, 107*(4), 569. doi:10.1038/ajg.2011.425

Wang, J. H., Wang, C. C., Hung, C. H., Chen, C. L., & Lu, S. N. (2012). Survival comparison between surgical resection and radiofrequency ablation for patients in BCLC very early/early stage hepatocellular carcinoma. *Journal of Hepatology, 56*(2), 412-418. doi:10.1016/j.jhep.2011.05.020

Chemoembolization

Brown, K. T., Do, R. K., Gonen, M., Covey, A. M., Getrajdman, G. I., Sofocleous, C. T., … Abou-Alfa, G., K. (2016). Randomized trial of hepatic artery embolization for hepatocellular carcinoma using doxorubicin-eluting microspheres compared with embolization with microspheres alone. *Journal of Clinical Oncology, 34*(17), 2046. doi:10.1200/JCO.2015.64.0821

Burrel, M., Reig, M., Forner, A., Barrufet, M., de Lope, C. R., Tremosini, S., … Bruix, J. (2012). Survival of patients with hepatocellular carcinoma treated by transarterial chemoembolisation (TACE) using Drug Eluting Beads. Implications for clinical practice and trial design. *Journal of Hepatology, 56*(6), 1330-1335. doi:10.1016/j.jhep.2012.01.008

Kudo, M., Han, G., Finn, R. S., Poon, R. T., Blanc, J. F., Yan, L., … Wang, J. (2014). Brivanib as adjuvant therapy to transarterial chemoembolization in patients with hepatocellular carcinoma: A randomized phase III trial. *Hepatology, 60*(5), 1697-1707. doi:10.1002/hep.27290

Lencioni, R., Llovet, J. M., Han, G., Tak, W. Y., Yang, J., Guglielmi, A., … Bruix, J. (2016). Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: The SPACE trial. *Journal of Hepatology, 64*(5), 1090-1098. doi:10.1016/j.jhep.2016.01.012

Lo, C. M., Ngan, H., Tso, W. K., Liu, C. L., Lam, C. M., Poon, R. T. P., … Wong, J. (2002). Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology, 35*(5), 1164 1171. doi:10.1053/jhep.2003.50047

Meyer, T., Fox, R., Ma, Y. T., Ross, P. J., James, M. W., Sturgess, R., … Daniel Palmer, D., H. (2017). Sorafenib in combination with transarterial chemoembolisation in patients with unresectable hepatocellular carcinoma (TACE 2): A randomised placebo-controlled, double-blind, phase 3 trial. *The Lancet Gastroenterology & Hepatology, 2*(8), 565-575. doi: 10.1016/S2468-1253(17)30156-5

Yao, F. Y., Kinkhabwala, M., LaBerge, J. M., Bass, N. M., Brown Jr, R., Kerlan, R., … Roberts, J. P. (2005). The impact of pre-operative loco-regional therapy on outcome after liver transplantation for hepatocellular carcinoma. *American Journal of Transplantation, 5*(4), 795-804. doi:10.1111/j.1600-6143.2005.00750.x

Continued on Next Page

SUGGESTED READINGS

Child-Pugh score

Pugh, R. N. H., Murray-Lyon, I. M., Dawson, J. L., Pietroni, M. C., & Williams, R. (1973). Transection of the oesophagus for bleeding oesophageal varices. *British Journal of Surgery*, *60*(8), 646-649.

CLIP score

The Cancer of the Liver Italian Program (CLIP) Investigators. (1998). A new prognostic system for hepatocellular carcinoma: A retrospective study of 435 patients. *Hepatology*, *28*(3), 751-755. doi:10.1002/hep.510280322

Radiofrequency Ablation (RFA)

Hong, S. N., Lee, S. Y., Choi, M. S., Lee, J. H., Koh, K. C., Paik, S. W., … Joh, J.W. (2005). Comparing the outcomes of radiofrequency ablation and surgery in patients with a single small hepatocellular carcinoma and well-preserved hepatic function. *Journal of Clinical Gastroenterology*, *39*(3), 247-252. doi: 10.1097/01.mcg.0000152746.72149.31

Mazzaferro, V., Battiston, C., Perrone, S., Pulvirenti, A., Regalia, E., Romito, R., … Andreola, S. (2004). Radiofrequency ablation of small hepatocellular carcinoma in cirrhotic patients awaiting liver transplantation: A prospective study. *Annals of Surgery*, *240*(5), 900-909. doi:10.1097/01.sla.0000143301.56154.95

Pompili, M., Mirante, V. G., Rondinara, G., Fassati, L. R., Piscaglia, F., Agnes, S., … Rapaccini, G. L. (2005). Percutaneous ablation procedures in cirrhotic patients with hepatocellular carcinoma submitted to liver transplantation: Assessment of efficacy at explant analysis and of safety for tumor recurrence. *Liver Transplantation*, *11*(9), 1117-1126. doi:10.1002/lt.20469

Vivarelli, M., Guglielmi, A., Ruzzenente, A., Cucchetti, A., Bellusci, R., Cordiano, C., & Cavallari, A. (2004). Surgical resection versus percutaneous radiofrequency ablation in the treatment of hepatocellular carcinoma on cirrhotic liver. *Annals of Surgery*, *240*(1), 102-107. doi:10.1097/01.sla.0000129672.51886.44

Radiation therapy

Chadha, A. S., Gunther, J., R., Hsieh, C., Aliru, M., Mahadevan, L. S., Venkatesulu, B. P., … Krishnan, S. (2019) Proton beam therapy outcomes for localized unresectable hepatocellular carcinoma. *Radiotherapy and Oncology, 4*(133), 54-61. doi: 10.1016/j.radonc.2018.10.041

Holliday, E. B., Tao, R., Brownlee, Z., Das, P., Krishnan, S., Taniguchi, C., … Koay, E. J. (2017). Definitive radiation therapy for hepatocellular carcinoma with portal vein tumor thrombus. *Clinical and Translational Radiation Oncology, 7*(4), 39-45. doi: 10.1016/j.ctro.2017.04.003

Hong, T. S., Wo, J. Y., Yeap, B. Y., Ben-Josef, E., McDonnell, E. I., Blaszkowsky, L. S., … Zhu, A. X. (2015). Multi-Institutional Phase II Study of High-Dose Hypofractionated Proton Beam Therapy in Patients With Localized, Unresectable Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma. *Journal of Clinical Oncology, 34*(5):460-8. doi:10.1200/JCO.2015.64.2710

Krishnan, S., Dawson, L. A., Seong, J., Akine, Y., Beddar, S., Briere, T. M., … Mornex, F. (2008). Radiotherapy for hepatocellular carcinoma: An overview. *Annals of Surgical Oncology*, *15*(4), 1015-1024. doi:10.1245/s10434-007-9729-5

Continued on Next Page

SUGGESTED READINGS - continued

Radioembolization

Dhondt, E., Lambert, B., Hermie, L., Huyck, L., Vanlangenhove, P., Geerts, A., … Defreyne, L. (2022). 90Y Radioembolization versus Drug-eluting Bead Chemoembolization for Unresectable Hepatocellular Carcinoma: Results from the TRACE Phase II Randomized Controlled Trial. Radiology, 303(3), 699–710. https://doi.org/10.1148/radiol.211806

Golfieri, R., Mosconi, C., Cappelli, A., Giampalma, E., Galaverni, M. C., Pettinato, C., … Trevisani, F. (2015). Efficacy of radioembolization according to tumor morphology and portal vein thrombosis in intermediate–advanced hepatocellular carcinoma. *Future Oncology, 11*(23), 3133-3142. doi: 10.2217/fon.15.267

Gordon, A. C., Gabr, A., Riaz, A., Uddin, O. M., Abouchaleh, N., Ali, R., … Lewandowski, R. J. (2018). Radioembolization super survivors: Extended survival in non-operative hepatocellular carcinoma. *Cardiovascular and Interventional Radiology, 41*(10), 1557-1565. doi:10.1007/s00270-018-2008-y

Salem, R., Gabr, A., Riaz, A., Mora, R., Ali, R., Abecassis, M., … Lewandowski, R., J. (2018). Institutional decision to adopt Y90 as primary treatment for hepatocellular carcinoma informed by a 1,000-patient 15-year experience. *Hepatology, 68*(4), 1429-1440. doi:10.1002/hep.29691

Salem, R., Gordon, A. C., Mouli, S., Hickey, R., Kallini, J., Gabr, A., … Yaghmai, V. (2016). Y90 radioembolization significantly prolongs time to progression compared with chemoembolization in patients with hepatocellular carcinoma. *Gastroenterology, 151*(6), doi:1155-1163.10.1053/j.gastro.2016.08.029

Salem, R., Johnson, G. E., Kim, E., Riaz, A., Bishay, V., Boucher, … Padia, S. A. (2021). Yttrium-90 Radioembolization for the Treatment of Solitary, Unresectable HCC: The LEGACY Study. Hepatology (Baltimore, Md.), 74(5), 2342–2352. https://doi.org/10.1002/hep.31819

Salem, R., Padia, S. A., Lam, M., Bell, J., Chiesa, C., Fowers, K., … Etienne Garin, E. (2019). Clinical and dosimetric considerations for Y90: Recommendations from an international multidisciplinary working group. *European Journal of Nuclear Medicine and Molecular Imaging, 46*(8), 1695-1704. doi:10.1007/s00259-019-04340-5

Vilgrain, V., Pereira, H., Assenat, E., Guiu, B., Ilonca, A., D., Pageaux, G., P., … Marthey, L. (2017). Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): An open-label randomised controlled phase 3 trial. *The Lancet Oncology, 18*(12), 1624-1636. doi: 10.1016/S1470-2045(17)30683-6

Surgery

Andreou, A., Vauthey, J. N., Cherqui, D., Zimmitti, G., Ribero, D., Truty, M. J., … Belghiti, J. (2013). Improved long-term survival after major resection for hepatocellular carcinoma: A multicenter analysis based on a new definition of major hepatectomy. *Journal of Gastrointestinal Surgery, 17(1)*, 66-77. doi:10.1007/s11605-012-2005-4

Inoue, Y., Hasegawa, K., Ishizawa, T., Aoki, T., Sano, K., Beck, Y., … Makuuchi, M. (2009). Is there any difference in survival according to the portal tumor thrombectomy method in patients with hepatocellular carcinoma?. *Surgery, 145*(1), 9-19. doi:10.1016/j.surg.2008.09.005

Ishizawa, T., Hasegawa, K., Aoki, T., Takahashi, M., Inoue, Y., Sano, K., … Makuuchi, M. (2008). Neither multiple tumors nor portal hypertension are surgical contraindications for hepatocellular carcinoma. *Gastroenterology, 134*(7), 1908-1916. doi:10.1053/j.gastro.2008.02.091

Kokudo, T., Hasegawa, K., Yamamoto, S., Shindoh, J., Takemura, N., Aoki, T., & Kokudo, N. (2014). Surgical treatment of hepatocellular carcinoma associated with hepatic vein tumor thrombosis. *Journal of Hepatology, 61*(3), 583-588. doi:10.1016/j.jhep.2014.04.032

Mazzaferro, V., Regalia, E., Doci, R., Andreola, S., Pulvirenti, A., Bozzetti, F., … Gennari, L. (1996). Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *New England Journal of Medicine*, *334*(11), 693-699. doi:10.1056/NEJM199603143341104

Continued on Next Page

SUGGESTED READINGS - continued

Surgery - continued

Minagawa, M., Ikai, I., Matsuyama, Y., Yamaoka, Y., & Makuuchi, M. (2007). Staging of hepatocellular carcinoma: assessment of the Japanese TNM and AJCC/UICC TNM systems in a cohort of 13,772 patients in Japan. *Annals of Surgery*, *245*(6), 909-922. doi:10.1097/01.sla.0000254368.65878.da

Palavecino, M., Chun, Y. S., Madoff, D. C., Zorzi, D., Kishi, Y., Kaseb, A. O., … Vauthey, J. N. (2009). Major hepatic resection for hepatocellular carcinoma with or without portal vein embolization: Perioperative outcome and survival. *Surgery*, *145*(4), 399-405. doi:10.1016/j.surg.2008.10.009

Pawlik, T. M., Poon, R. T., Abdalla, E. K., Zorzi, D., Ikai, I., Curley, S. A., … Vauthey, J. N. (2005). Critical appraisal of the clinical and pathologic predictors of survival after resection of large hepatocellular carcinoma. *Archives of Surgery*, *140*(5), 450-457. doi:10.1001/archsurg.140.5.450

Shindoh, J., Makuuchi, M., Matsuyama, Y., Mise, Y., Arita, J., Sakamoto, Y., & Kokudo, N. (2016). Complete removal of the tumor-bearing portal territory decreases local tumor recurrence and improves disease-specific survival of patients with hepatocellular carcinoma. *Journal of Hepatology, 64*(3), 594-600. doi:10.1016/j.jhep.2015.10.015

Shindoh, J., Tzeng, C. W. D., & Vauthey, J. N. (2012). Portal vein embolization for hepatocellular carcinoma. *Liver cancer, 1*(3-4), 159-167. doi:10.1159/000343829

Torzilli, G., Belghiti, J., Kokudo, N., Takayama, T., Capussotti, L., Nuzzo, G., … Morenghi, E. (2013). A snapshot of the effective indications and results of surgery for hepatocellular carcinoma in tertiary referral centers: Is it adherent to the EASL/AASLD recommendations? An observational study of the HCC East-West study group. *Annals of Surgery, 257*(5), 929-937.doi:10.1097/SLA.0b013e31828329b8

Torzilli, G., Donadon, M., Marconi, M., Botea, F., Palmisano, A., Del Fabbro, D., … Montorsi, M. (2008). Systematic extended right posterior sectionectomy: a safe and effective alternative to right hepatectomy. *Annals of Surgery, 247*(4), 603-611.doi:10.1097/SLA.0b013e31816387d7

Torzilli, G., Procopio, F., Viganò, L., Costa, G., Fontana, A., Cimino, M., … Del Fabbro, D. (2019). The liver tunnel: Intention-to-treat validation of a new type of hepatectomy. *Annals of Surgery, 269(2)*, 331-336. doi:10.1097/SLA.0000000000002509

Vauthey, J. N., Lauwers, G. Y., Esnaola, N. F., Do, K. A., Belghiti, J., Mirza, N., … Nagorney, D. M. (2002). Simplified staging for hepatocellular carcinoma. *Journal of Clinical Oncology*, *20*(6), 1527-1536. doi:10.1200/JCO.2002.20.6.1527

Systemic Therapy

Abou-Alfa, G. K., Lau, G., Kudo, M., Chan, S. L., Kelley, R. K., Furuse, J., … Sangro, B. (2022). Tremelimumab plus Durvalumab in Unresectable Hepatocellular Carcinoma. *New England Journal of Medicine*, *Evidence, 1*(8). doi:10.1056/EVIDoa2100070

Abou-Alfa, G. K., Meyer, T., Cheng, A. L., El-Khoueiry, A. B., Rimassa, L., Ryoo, B. Y., … Blanc, J. F. (2018). Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. *New England Journal of Medicine*, *379*(1), 54-63. doi:10.1056/NEJMoa1717002

Bruix, J., Qin, S., Merle, P., Granito, A., Huang, Y. H., Bodoky, G., … Han, G. (2017). Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESOURCE): A randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet, 238*(10064), 56-66. doi:10.1016/S0140-6736(16)32453-9

Cheng, A. L., Kang, Y. K., Chen, Z., Tsao, C. J., Qin, S., Kim, J. S., … Guan, Z. (2009). Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: A phase III randomised, double-blind, placebo-controlled trial. *The Lancet Oncology*, *10*(1), 25-34. doi:10.1016/S1470-2045(08)70285-7

Cheng, A. L., Qin, S., Ikeda, M., Galle, P., Ducreux, M., Zhu, A., … Kaseb, A. (2019). IMbrave150: Efficacy and safety results from a ph III study evaluating atezolizumab (atezo)+ bevacizumab (bev) vs sorafenib (Sor) as first treatment (tx) for patients (pts) with unresectable hepatocellular carcinoma (HCC). *Annals of Oncology, 30*, ix186-ix187.

Continued on Next Page

SUGGESTED READINGS - continued

Systemic Therapy – continued

El-Khoueiry, A. B., Sangro, B., Yau, T., Crocenzi, T. S., Kudo, M., Hsu, C., … Melero, I. (2017). Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): An open-label, non-comparative, phase ½ dose escalation and expansion trial. *The Lancet, 389*(10088), 2492-2502. doi:10.1016/S0140-6736(17)31046-2

Kudo, M., Finn, R. S., Qin, S., Han, K. H., Ikeda, K., Piscaglia, F., … Cheng, A. L. (2018). Lenvatinib versus sorafenib in first-line treatment with unresectable hepatocellular carcinoma: A randomised phase 3 non-inferiority trial. *The Lancet, 391*(10126), 1163-1173. doi:10.1016/S0140-6736(18)30207-1

Llovet, J. M., Ricci, S., Mazzaferro, V., Hilgard, P., Gane, E., Blanc, J.-F., … Bruix, J. (2008). Sorafenib in advanced hepatocellular carcinoma. The *New England Journal of Medicine*, *359*(4), 378-390. doi:10.1056/NEJMoa0708857

National Comprehensive Cancer Network. (2022). *Hepatobiliary Cancers* (NCCN Guideline Version 3.2022). Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf

Schwarz, R. E., Abou-Alfa, G. K., Geschwind, J. F., Krishnan, S., Salem, R., & Venook, A. P. (2010). Nonoperative therapies for combined modality treatment of hepatocellular cancer: Expert consensus statement. J*ournal of the International Hepato Pacreato Biliary Association, 12*(5), 313-320. doi:10.1111/j.1477-2574.2010.00183.x

Zhu, A. X., Finn, R. S., Edeline, J., Cattan, S., Ogasawara, S., Palmer, D., … Kudo, M. (2018). Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): A non-randomised, open-label phase 2 trial. *The Lancet, 19*(7), 940-952. doi:10.1016/S1470-2045(18)30351-6

Zhu, A. X., Kang, Y. K., Yen, C. J., Finn, R. S., Galle, P. R., Llovet, J. M., … Rau, K. M. (2019). Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): A randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet Oncology*, *20*(2), 282-296. doi:10.1016/S1470-2045(18)30937-9

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:

Core Development Team Leads

Ahmed O. Kaseb, MD (GI Medical Oncology)
Hyunseon Christine Kang, MD, PhD (Diagnostic Radiology – Abdominal Imaging)
Jean-Nicolas Vauthey, MD (Surgical Oncology)

Workgroup Members

Olga N. Fleckenstein, BS♦
Harmeet Kaur, MD (Diagnostic Radiology – Abdominal Imaging)
Eugene Koay, MD, PhD (GI Radiation Oncology)
Joshua Kuban, MD (Interventional Radiology)
Sunyoung Lee, MD, PhD (GI Medical Oncology)
Armeen Mahvash, MD (Interventional Radiology)
Ethan Miller, MD (Gastroenterology Hepat & Nutr)
Van Nguyen, PharmD (Pharmacy Clinical Programs)
Bruno Odisio, MD (Interventional Radiology)
Sireesha Yedururi, MBBS (Diagnostic Radiology – Abdominal Imaging)
Milena Zhang, PharmD♦

♦ Clinical Effectiveness Development Team