Submitted by:
Gregory Nadolski, MD, University of Pennsylvania
Sid Padia, MD, UCLA Health
Amanda Smolock, MD, PhD, Medical College of Wisconsin
Beau Toskich, MD, Mayo Clinic Comprehensive Cancer Center

Organization:
Society of Interventional Oncology
2025 M St NW #800, Washington, DC 20036
Phone: (202) 367-1164
Email: HMuerhoff@sio-central.org

September 30, 2022
NCCN Guidelines Panel: Hepatobiliary Cancer

On behalf of the Society of Interventional Oncology, we respectfully request the NCCN Guidelines Panel for Hepatobiliary Cancer review the enclosed recommendations:

Specific Change 1: Thermal ablation should be added as an additionally preferred first line treatment for eligible patients with very early-stage HCC who are not candidates for liver transplantation (HCC-4).

Rationale: Thermal ablation is listed as a firs line treatment in patients with early-stage HCC who are not candidates for liver transplantation in the BCLC guidelines. The SURF phase 3 randomized controlled trial demonstrated that overall survival and recurrence free survival were not significantly different between patients undergoing surgery versus radiofrequency ablation for small HCC (≤ 3 cm and 3 nodules). (Reig M et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. J Hepatol. 2022 Mar;76(3):681-693. doi: 10.1016/j.jhep.2021.11.018. Epub 2021 Nov 19. PMID: 34801630; PMCID: PMC8866082) (Takayama T et al. Surgery versus Radiofrequency Ablation for Small Hepatocellular Carcinoma: A Randomized Controlled Trial (SURF Trial). Liver Cancer. 2021 Dec 29;11(3):209-218. doi: 10.1159/000521665. PMID: 35949295; PMCID: PMC9218617) (10.1200/JCO.2021.39.15_suppl.4093 Journal of Clinical Oncology 39, no. 15_suppl (May 20, 2021) 4093-4093).

Specific Change 2: The discussion should mention that radioembolization should be considered in lieu of transarterial chemoembolization for solitary HCC <8 cm in patients with CPA liver function.

Rationale: The LEGACY study demonstrated safety and efficacy of selective high dose radioembolization for the treatment of solitary HCC up to 8cm which was subsequently followed with FDA approval for this indication. The 2022 BCLC recommendations now have incorporated radioembolization as a recommended therapy for BCLC A disease that is not amenable to surgery or thermal ablation. (Salem R et al. Yttrium-90 Radioembolization for the Treatment of Solitary, Unresectable HCC: The LEGACY Study. Hepatology. 2021 Nov;74(5):2342-2352. doi: 10.1002/hep.31819. Epub 2021 Jun 11. PMID: 33739462; PMCID: PMC8596669) (Reig M et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. J Hepatol. 2022 Mar;76(3):681-693. doi: 10.1016/j.jhep.2021.11.018. Epub 2021 Nov 19. PMID: 34801630; PMCID: PMC8866082).

The results of the TRACE phase 2 randomized controlled trial met its primary endpoint of overall time to progression in favor of radioembolization versus drug eluting bead chemoembolization (17.1 months in the TARE

arm versus 9.5 months in the DEB-TACE arm [HR], 0.36; 95% CI: 0.18, 0.70; P = .002). It met its secondary endpoint of superior survival as well (30.2 months after TARE and 15.6 months after DEB-TACE HR, 0.48; 95% CI: 0.28, 0.82; P = .006). There was no difference in serious adverse events between cohorts (P=0.47). (Dhondt E et al. 90Y Radioembolization versus Drug-eluting Bead Chemoembolization for Unresectable Hepatocellular Carcinoma: Results from the TRACE Phase II Randomized Controlled Trial. Radiology. 2022 Jun;303(3):699-710. doi: 10.1148/radiol.211806. Epub 2022 Mar 8. PMID: 35258371.)

This is additionally support to a previous phase 2 randomized clinical trial which met its primary endpoint of superior time to progression in favor of radioembolization versus conventional chemoembolization (>26 mo vs. 6.8 mo; P = .0012 [HR] 0.122; 95% CI: 0.027-0.557; P = .007). (Salem R et al. Y90 Radioembolization Significantly Prolongs Time to Progression Compared With Chemoembolization in Patients With Hepatocellular Carcinoma. Gastroenterology. 2016 Dec;151(6):1155-1163.e2. doi: 10.1053/j.gastro.2016.08.029. Epub 2016 Aug 27. PMID: 27575820; PMCID: PMC5124387).

Specific change 3: Radiation segmentectomy should be described as an ablative form of radiation therapy with treatment recommendations in HCC-E (1), as are similarly present for SBRT in plate HCC-F (1). A dose of >400 Gy to 25% of the liver or less in patients with Child Pugh A liver function is recommended.

Rationale: These outcomes are supported by the LEGACY study, in addition to the recent RASER study and existing radiopathologic evidence. (Kim E et al. Radiation segmentectomy for curative intent of unresectable very early to early-stage hepatocellular carcinoma (RASER): a single-centre, single-arm study. Lancet Gastroenterol Hepatol. 2022 Sep;7(9):843-850. doi: 10.1016/S2468-1253(22)00091-7. Epub 2022 May 23. PMID: 35617978) (Montazeri SA, De la Garza-Ramos et al. Hepatocellular carcinoma radiation segmentectomy treatment intensification prior to liver transplantation increases rates of complete pathologic necrosis: an explant analysis of 75 tumors. Eur J Nucl Med Mol Imaging. 2022 Sep;49(11):3892-3897. doi: 10.1007/s00259-022-05776-y. Epub 2022 Apr 20. PMID: 35441860).

Specific Change 4: The 5th bullet point mentioning Sorafenib should be moved to principals of systemic therapy HCC-G. Within the discussion, mention should be made of TACE in conjunction with lenvatinib as a demonstrating a benefit in survival when compared to lenvatinib monotherapy alone for the treatment of advanced HCC.

Rationale: Sorafenib is no longer a first line systemic therapy agent. Mention of its use in the transarterial therapies section holds little relevance to current practice and is best allocated to discussion of systemic therapy.

The phase 3 randomized LAUNCH trial supported the use of TACE plus lenvatinib vs lenvatinib alone for advanced HCC (17.8 v 11.5 months; hazard ratio, 0.45; P < .001). (Peng Z et al. Lenvatinib Combined With Transarterial Chemoembolization as First-Line Treatment for Advanced Hepatocellular Carcinoma: A Phase III, Randomized Clinical Trial (LAUNCH). J Clin Oncol. 2022 Aug 3:JCO2200392. doi: 10.1200/JCO.22.00392. Epub ahead of print. No pages yet. PMID: 35921605).

Furthermore, prospective trials suggest TACE plus lenvatinib is superior to TACE plus sorafenib in patients with BCLC C disease. In an open-label, single-center, randomized trial (ClinicalTrials.gov identifier: NCT04127396), patients with treatment naive HCC and portal vein tumor thrombus (PVTT) were randomized 1:1 to receive TACE plus lenvatinib or TACE plus sorafenib. The primary end point was TTP and secondary end points included ORR and toxicity. In total, 64 patients were randomized (lenvatinib, n = 32; sorafenib, n = 32); most patients had branch PVTT (71.9%), and the median target tumor diameter was 9.8 cm (range, 3.8-21.8). Median TTP was 4.7 for TACE plus lenvatinib vs 3.1 months for TACE plus sorafenib (HR, 0.55; 95% CI, 0.32-0.95; P = .029) and ORR was 53.1% in the lenvatinib arm compared to 25.0% in sorafenib arm (P = .039). Multivariable analysis showed that TACE plus lenvatinib was significantly associated with higher TTP versus TACE plus sorafenib (HR, 0.50; 95% CI, 0.28-0.90; P = .021). Comparable safety profiles were observed in both arms demonstrating that TACE plus lenvatinib was safe, well tolerated, and had favorable efficacy versus TACE plus sorafenib in patients with advanced HCC with PVTT and large tumor burden. (Ding, X et al. Cancer 2021 Oct 15;127(20):3782-3793. doi: 10.1002/cncr.33677. Epub 2021 Jul 8.)

Specific Change 5: As is mentioned for EBRT, Cryoblation should be added to principals of locoregional therapy under ablation HCC-E (1) as an effective means of treatment for painful osseous metastases.

Rationale: The MOTION multicenter, prospective, single-arm study of cryoablation for painful osseous metastases demonstrated rapid and durable pain palliation and provided an alternative to opioid use with improved quality of life. (Jennings JW et al. Cryoablation for Palliation of Painful Bone Metastases: The MOTION Multicenter Study. Radiol Imaging Cancer. 2021 Feb 12;3(2):e200101. Pg 1-11;doi: 10.1148/rycan.2021200101. PMID: 33817650; PMCID: PMC8011449).

Thank you for your consideration of these recommendations.

Sincerely,

Gregory Nadolski, MD
Sid Padia, MD
Amanda Smolock, MD, PhD
Beau Toskich, MD