Editorial Commentary

Global similarities: comparison of the Korean Liver Cancer Association chemoembolization guidelines for hepatocellular carcinoma to the National Comprehensive Cancer Network, American Association for the Study of Liver Diseases and Barcelona Clinic Liver Cancer recommendations

Meaghan S. Dendy Case, Daniel B. Brown^

Department of Radiology and Radiologic Sciences, Vanderbilt University Medical Center, Nashville, TN, USA

Correspondence to: Daniel B. Brown, MD. Department of Radiology and Radiologic Sciences, Vanderbilt University Medical Center, 1161 21st Ave S, CCC-1118 Medical Center North, Nashville, TN 37232, USA. Email: daniel.b.brown@vumc.org.

Comment on: Cho Y, Choi JW, Kwon H, *et al.* Transarterial chemoembolization for hepatocellular carcinoma: 2023 expert consensus-based practical recommendations of the Korean Liver Cancer Association. J Liver Cancer 2023;23:241-61.

Keywords: Hepatocellular carcinoma (HCC); therapeutic chemoembolization; interventional radiology

Submitted Jan 09, 2024. Accepted for publication Feb 01, 2024. Published online Mar 26, 2024.

doi: 10.21037/hbsn-24-12

View this article at: https://dx.doi.org/10.21037/hbsn-24-12

Hepatocellular carcinoma (HCC) remains the third most common cause of cancer-related deaths worldwide (1). Transarterial chemoembolization (TACE) has been established as a therapeutic option in those patients who are outside of surgical resection or transplant criteria for over four decades (2). Multiple expert panels have outlined the appropriate use criteria and recommendations for HCC treatment (3-5). These documents have focused on multiple treatment modalities including interventional radiology intra-arterial and ablative treatments as well as resection, transplant and systemic therapy. In their recently published practice recommendations for the use of TACE in HCC patients, the Korean Liver Cancer Association (KLCA) has developed a comprehensive list of recommendations for this specific modality (6). The recommendations are a combination of evidence-based, expert consensus decisions and surveys of Korean experts in TACE for HCC. Comparing and contrasting this focused guideline on TACE to the recent HCC guidelines from the National Comprehensive Cancer Network (NCCN), American Association for the Study of Liver Diseases (AASLD) and Barcelona Clinic Liver Cancer (BCLC) is valuable to understand where methods are truly global and also to understand differences in treatment approach by region.

Pre- and post-treatment management

Key points regarding pre- and post-procedure management are similar to the other documents and include:

(I) Pre-treatment contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) should be performed within 2 months prior to the scheduled procedure.

(II) Prophylactic antibiotics should be considered in those patients with biliary obstruction, stenting across the ampulla of Vater and pre-existing bilioenteric anastomosis.

(III) Both celiac and superior mesenteric artery angiography is useful at the initial procedure. Cone beam CT is also recommended to increase efficacy

^ ORCID: 0000-0003-0533-2883.

and safety of treatment.

(IV) Intra-arterial lidocaine to limit post-embolization syndrome is used by 49.1% of surveyed interventional radiologists.

(V) The authors correctly outline that post embolization syndrome should be managed based on specific procedure-related symptoms such as pain and nausea. Routine steroid use is not common.

(VI) Response assessment should be performed 4–8 weeks after treatment. CT has the added benefit of evaluating lipiodol coverage of the tumor.

Treatment details

The KLCA document states that TACE is the recommended first-line treatment for HCC patients with preserved liver function, good performance status and no evidence of vascular invasion or metastatic disease when curative therapies such as resection, transplantation or ablation are not an option (6). Cho *et al.* dive deeper into technical details of HCC chemoembolization than the other documents although some parallels are identifiable. The recommendations for superselective TACE are mirrored in the AASLD guidelines where subsegmental or segmental treatment is preferable to lobar treatment at the strongest level of recommendation (3,6). The dedication to distal catheterization goes beyond treatment of single small tumors. Survey outcomes demonstrated that superselective TACE was performed by 72% of responders for solitary <3 cm HCC, for 69.7% of HCC within Milan criteria and 34.8% of multinodular HCC with all less than 5 cm.

Cho *et al.* also provide details regarding microcatheter selection. In the current standards document, 60.6% of operators used a 1.5–1.7 Fr microcatheter and >95% used a microcatheter <2.0 Fr. Based on existing data, operator experience and patient anatomy. Smaller devices permit greater flow around the microcatheter while infusing embolics, maximizing downstream delivery. The authors also recommend maximum doses/volumes of lipiodol (15 mL), doxorubicin (preferably 50 mg) and cisplatin (2 mg/kg, maximum 200 mg) per session of conventional transarterial chemoembolization (cTACE) (6). Dosing recommendation for drug-eluting bead (DEB)-TACE is of 100 mg of doxorubicin per session (6).

The AASLD, NCCN and BCLC guidelines do not compare DEB-TACE and cTACE outcomes and toxicities (3-5). Cho *et al.* report that while DEB-TACE may have a pharmacokinetic advantage, differences in tumor response, time to progression, overall and survival are not consistently identified. Moreover, patients with smaller tumors may have lower response rates with 100–300-micron DEB compared to cTACE based on two prospective trials:

(I) Specifically, a prospective multicenter trial in Korea resulted in similar responses between DEB-TACE and cTACE for tumors 2–5 cm with cTACE having superior outcomes when ≤2 cm (7).

(II) A randomized controlled trial in Japan reported lower response rates with DEB-TACE in HCC ≤3 cm (8).

Future DEB-TACE research should utilize <150-micron microspheres. From the expert user survey, the most used embolic agent with cTACE is commercially available gelatin sponge particles, which are used by 93.2% of operators. These particles come in different sizes and 100–350 microns is the most used. Like DEB-TACE, there is an absence of standardization of particle size in relation to tumor size, vascularity, or level of subselection at the time of embolization. The endpoint of embolization remains non-quantitative as well, with operators relying primarily on absence of contrast clearance along with oil deposition in the sinusoids draining the tumor with more sluggish flow preferred with progressive distal catheter selection.

Areas where treatment approaches are evolving

The authors state that TACE for HCC with vascular invasion is an alternative, non-first line treatment. Management of invasive HCC is evolving with development of multiple lines of effective systemic therapy. By comparison:

(I) The NCCN guidelines state that arterial therapy is safe in highly selected HCC patients with limited portal vein involvement.

(II) The AASLD guidelines note that arterial therapy should be avoided in the setting of main portal or hepatic vein invasion.

(III) The BCLC guidelines describe systemic therapy as a treatment for patients with vascular invasion.

Of the existing guidelines, the AASLD guidelines recommend TACE as the primary treatment option for unresectable/unablatable HCC. Additionally, the AASLD document does not recommend TACE combined with systemic therapy outside the clinical trial setting. The NCCN guidelines do not recommend specific treatments when considering arterial treatment of HCC, referring to TACE and radioembolization collectively as “arterially directed therapy”. The BCLC document includes both

radioembolization and chemoembolization. The purpose of the current paper by Cho *et al.* was to focus on TACE alone. In future iterations, it would be useful to include some detail regarding applications for TACE *vs.* radioembolization or combining TACE with thermal ablation.

Identifying patients that are TACE refractory is an important part of HCC management given the evolution of systemic therapy. Cho *et al.* comment that TACE failure is typically due to non-selective/lobar treatment of bulkier disease (6). TACE refractoriness is described in the KLCA document as failure of objective response or new vascular invasion after two consecutive on demand chemoembolizations. The NCCN guidelines mention that systemic therapy should be considered when additional locoregional therapy is not feasible. The BCLC guidelines focus on the important consideration regarding whether progressive/new disease is in the zone of previous treatment. The AASLD guidelines include several variables including:

(I) Lack of objective response with >50% viable disease after two TACE sessions.
(II) New HCC developing in the treatment zone after two TACE sessions.
(III) Lack of improvement of tumor markers after two TACE sessions.
(IV) Stage migration to advanced or metastatic HCC.

All four guidelines are generally aligned regarding this issue. It is also important to recognize that beyond systemic therapy, TACE refractory HCC may also be treatable with radioembolization (9). As HCC management further expands into lines of therapy, recognizing opportunities based on local expertise, cost as well as tumor size, number, and presence/absence of portal venous invasion.

Summary

We would like to commend Cho and colleagues for this outstanding contribution to the existing guidelines on HCC management. The combination of survey data and technical details regarding TACE will make this document particularly useful to interventional radiologists.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Hepatobiliary Surgery and Nutrition*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-24-12/coif). D.B.B. reports research support from Guerbet and Sirtex Medical and he has done a podcast for Cook Medical. The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Siegel RL, Miller KD, Wagle NS, et al. Cancer statistics, 2023. CA Cancer J Clin 2023;73:17-48.
2. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet 2003;362:1907-17.
3. Singal AG, Llovet JM, Yarchoan M, et al. AASLD Practice Guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. Hepatology 2023;78:1922-65.
4. Benson AB, D'Angelica MI, Abbott DE, et al. Hepatobiliary Cancers, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2021;19:541-65.
5. Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. J Hepatol 2022;76:681-93.
6. Cho Y, Choi JW, Kwon H, et al. Transarterial chemoembolization for hepatocellular carcinoma: 2023 expert consensus-based practical recommendations of the Korean Liver Cancer Association. J Liver Cancer 2023;23:241-61.
7. Lee M, Chung JW, Lee KH, et al. Prospective Multi-Center Korean Registry of Transcatheter Arterial

Chemoembolization with Drug-Eluting Embolics for Nodular Hepatocellular Carcinoma: A Two-Year Outcome Analysis. Korean J Radiol 2021;22:1658-70.
8. Lee IJ, Lee JH, Lee YB, et al. Effectiveness of drug-eluting bead transarterial chemoembolization versus conventional transarterial chemoembolization for small hepatocellular carcinoma in Child-Pugh class A patients. Ther Adv Med Oncol 2019;11:1758835919866072.
9. Hund HC, Du L, Matsuoka L, et al. Effect of Previous Transarterial Chemoembolization on Survival and Toxicity after Yttrium-90 Transarterial Radioembolization of Hepatocellular Carcinoma in the Radiation-Emitting SIR-Spheres in Nonresectable Liver Tumor Registry. J Vasc Interv Radiol 2023;34:2147-2154.e2.

Cite this article as: Dendy Case MS, Brown DB. Global similarities: comparison of the Korean Liver Cancer Association chemoembolization guidelines for hepatocellular carcinoma to the National Comprehensive Cancer Network, American Association for the Study of Liver Diseases and Barcelona Clinic Liver Cancer recommendations. HepatoBiliary Surg Nutr 2024;13(2):343-346. doi: 10.21037/hbsn-24-12