



New developments in ablation therapy for hepatocellular carcinoma: combination with systemic therapy and radiotherapy

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Comment on: Cheung TT, Ma KW, She WH. A review on radiofrequency, microwave and high-intensity focused ultrasound ablations for hepatocellular carcinoma with cirrhosis. *Hepatobiliary Surg Nutr* 2021;10:193-209.

Submitted Aug 14, 2022. Accepted for publication Sep 05, 2022.

doi: 10.21037/hbsn-22-363

View this article at: <https://dx.doi.org/10.21037/hbsn-22-363>

We carefully read the review article, which compared three types of ablation therapies such as radiofrequency ablation (RFA), high-intensity focused ultrasound (HIFU), and microwave ablation (MWA) for Barcelona clinic liver cancer (BCLC) stage 0 and A (early-stage) hepatocellular carcinoma (HCC) patients with cirrhosis by Cheung *et al.* (1) published in 2021 in *Hepatobiliary Surgery and Nutrition*. This manuscript well described the principles, indications, and limitations of these ablation systems in detail (1). We would like to provide several comments.

In the comparison table indicated by the authors [*Tab. 4* in Ref. (1)], HIFU has a longer treatment time than RFA/MWA. On the other hand, it can treat HCCs with ascites or located behind the portal vein that are not suitable for RFA/MWA. HIFU ablation with the upper approach can compress the body compared to HIFU ablation with the lower approach, which is closer to the target lesion and easier to manipulate and may lead to a shorter treatment time. The HIFU device under development in Japan also uses the upper approach method.

Unlike HIFU, histotripsy is a non-thermal ablation therapy. Histotripsy utilizes focused ultrasound irradiated from outside the body to mechanically destroy tissues by cavitation, reducing targeted tumors to cell-free remnants in a short period of time. A phase I trial of histotripsy for the treatment of liver malignancies (NCT03741088) demonstrated the initial safety and efficacy of hepatic histotripsy and provided the first evidence of an absorbing effect that may be caused by histotripsy in humans (2).

Conventional RFA, MWA, and HIFU are indicated

up to early-stage HCC. As with HIFU, stereotactic body radiotherapy (SBRT) is now considered a treatment option for early-stage HCC, although the number of centers where SBRT can be performed is limited. SBRT is primarily indicated for lesions for which RFA is difficult, i.e., lesions that are difficult to puncture (just below the diaphragm, behind the portal vein, or adjacent to the relatively large portal vein and hepatic vein) (3). SBRT can be performed as an additional treatment for residual areas of transcatheter arterial chemoembolization (TACE) or RFA (3,4). When BCLC factors are appropriately adjusted, a meta-analysis revealed that SBRT has a comparable overall survival rate and superior local control rate compared to RFA (4). Thus, SBRT has a complementary role in the treatment of patients with HCC who are refractory to treatment with RFA (3,4).

In general, RFA can treat multiple HCCs in a single treatment, whereas SBRT can treat only one HCC unless multiple lesions are clustered in a single treatment. If there are three HCCs, where two of which are indicated for RFA but the remaining one is not, TACE is conventionally performed. However, the probability of TACE achieving complete necrosis is low. If SBRT is performed on the remaining lesion, complete necrosis of all lesions can be achieved (4,5). Wang *et al.* report that for eight patients with BCLC stage A4 and seven with BCLC stage B1, one HCC was treated with SBRT and the rest with RFA. The local control rate at 1 year was 97.4% (38/39 lesions). The median time to progression was 20.1 (2.8–45.1) months. 1- and 2-year survival rates were 100% and 88.9%,

Table 1 Studies of sorafenib + RFA and lenvatinib + RFA

	Arm	BCLC stage	CP class	Age (years)	Tumor size (cm)	Tumor number	TKI periods (day)	On/Off TKI with RFA	Results of efficacy
Sorafenib									
Fukuda (6)	RFA (N=30) SOR + RFA (N=15)	A	A, B	72.8	<3; 2.23±0.43	Single	7 days before RFA	No break	Ablated area (long- and short-axis dimensions); SOR + RFA is better
Feng (7)	RFA (N=64) SOR + RFA (N=64)	0-B1	A	49.7	≤7; 3.09±1.97	≤3	Within 60 days before or after RFA	No break	Recurrence rate OS; SOR + RFA is better
Kan (8)	RFA (N=32) SOR + RFA (N=30)	B, C	A, B	53.7	3.1–5.0	Single	After first RFA and continuous before or after the new RFA	No break	Recurrence rate, time to progression; SOR + RFA is better
Gong (9)	RFA (N=50) SOR + RFA (N=40)	A	A	55.7	2.6±1.4	1.4	28 days after RFA	–	Tumor-free survival, relapse rate, survival rate; SOR + RFA is better
Lenvatinib									
Wang (10)	LEN (N=13) LEN + RFA (N=9)	B2	A	76.1	4.8±3.2	4 (1–12)	Additional RFA: about 3 months after start of lenvatinib	4 days off: pre RFA; 7–10 days on: post RFA	Best response, PFS, OS; LEN + RFA is better

RFA, radiofrequency ablation; BCLC, Barcelona clinic liver cancer; CP, Child-Pugh; TKI, tyrosine kinase inhibitor; SOR, sorafenib; LEN, lenvatinib; OS, overall survival; PFS, progression free survival.

respectively. No patient showed serious complications after up to 5 months of observation. For patients with BCLC stage A4-B1, RFA and SBRT treatment are potential options for different multifocal HCCs because of their good prognosis and safety (5).

Additionally, several systemic therapies are now available for the treatment of HCC. The combination of systemic therapy and conventional RFA (with the addition of SBRT in some cases) may be able to treat up to BCLC stage B HCC (intermediate-stage HCC).

Table 1 presents manuscripts that have performed comparisons between RFA alone and sorafenib plus RFA (6-9), or lenvatinib alone and lenvatinib plus RFA (10). The addition of sorafenib to RFA ablated a larger area than RFA alone (6) and improved local recurrence rates and overall survival (7-9). The effect of sorafenib may have reduced tumor blood flow, resulting in a larger area for RFA ablation (6). The combination of RFA and sorafenib, rather than sorafenib alone, has the potential to reduce the tumor volume of viable HCC especially in intermediate-stage HCC, which may have led to improved recurrence rates and prognosis.

Lenvatinib became available in 2018. Compared to sorafenib, lenvatinib can markedly reduce tumor blood flow in HCC. Wang *et al.* reported that lenvatinib first-line therapy followed by RFA may be a viable option for intermediate-stage HCC patients with good liver function but a high tumor burden, given the better tumor response, improved survival, and similar safety profile compared to lenvatinib alone (10). To avoid the possibility of cumulative adverse events, patients in this combination group received additional RFA approximately 3 months after starting lenvatinib. If the initial lenvatinib plus RFA treatment did not lead to a complete response because the residual lesions were still too high or the target lesion was large, lenvatinib treatment was restarted at a relatively low dose to prevent local recurrence or distant metastasis, and then RFA was added (10).

This is just our speculation, but for multiple HCC cases, lenvatinib increases the extent of tumor thermal coagulation by RFA by reducing tumor blood flow. Between RFA and RFA, lenvatinib is used to suppress HCC growth (*Figure 1A*). For large and multiple HCC cases, after RFA, SBRT is added for sites that are difficult to puncture and

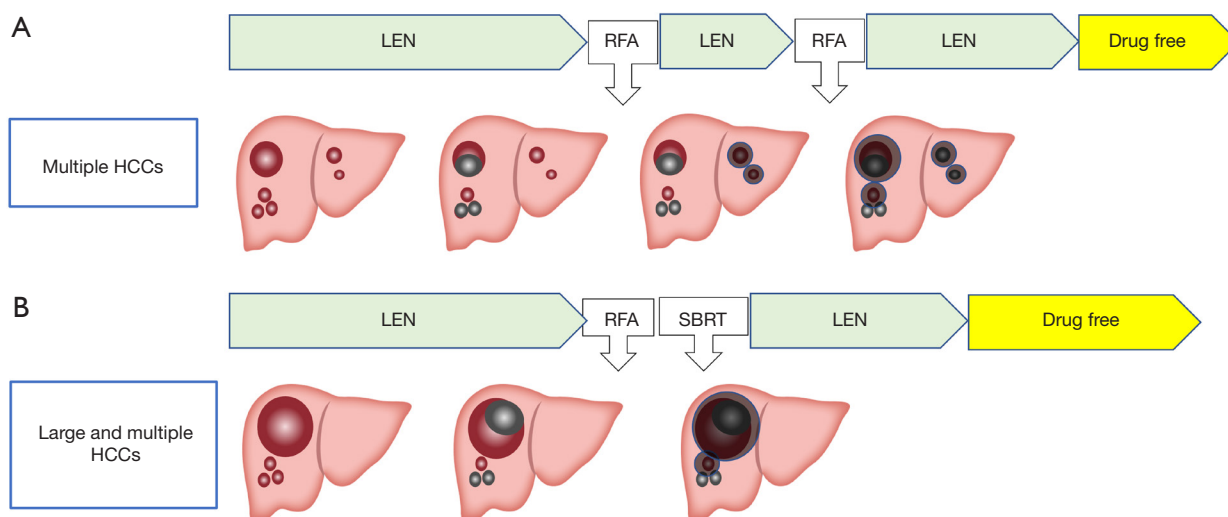


Figure 1 Sequential treatment of multiple and large hepatocellular carcinomas with LEN, RFA, and SBRT for complete necrosis. (A) For multiple HCC cases: lenvatinib increases the extent of tumor thermal coagulation by RFA by reducing tumor blood flow; between RFA and RFA, lenvatinib is used to suppress HCC growth. (B) For large and multiple HCC cases: After RFA, SBRT is added for sites that are difficult to puncture and cannot be suppressed with lenvatinib. LEN, lenvatinib; RFA, radiofrequency ablation; SBRT, stereotactic body radiotherapy; HCC, hepatocellular carcinoma.

cannot be suppressed with lenvatinib (*Figure 1B*). These sequential treatments of multiple and large HCCs with lenvatinib and RFA have the possibility of achieving complete necrosis.

In conclusion, the development of focused ultrasound has the potential to significantly reduce ablation time. RFA in combination with systemic therapy and/or SBRT may expand the indications for treatment to intermediate-stage HCC. Further research is needed to support these newly introduced treatments. Combination therapy of MWA or HIFU with systemic therapy or SBRT should be tried in the future.

Acknowledgments

Funding: This research was supported by the National Natural Science Foundation of China (No. 82102074) Key Science and Technology Program of Shaanxi Province of China (No. 2022SF-320).

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office of *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-22-363/coif>). The authors have 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.

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Cite this article as: Numata K, Wang F. New developments in ablation therapy for hepatocellular carcinoma: combination with systemic therapy and radiotherapy. *HepatoBiliary Surg Nutr* 2022;11(5):766-769. doi: 10.21037/hbsn-22-363