Editorial Commentary

Microwave ablation in solitary hepatocellular carcinoma within 3–5 cm requiring consideration

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Hepatocellular carcinoma (HCC) is a global health issue and remains the second most common cause of cancer-related deaths (1). With in-depth research in this field, treatment options are becoming more diverse. Liver resection, thermal ablation, and transplantation could offer a curative chance in early HCC. Locoregional ablation therapy, including radiofrequency ablation (RFA), microwave ablation (MWA), etc., is a proven cure tactic for early-stage HCC. Meanwhile, MWA may provide superior tumor control over RFA and other ablations for patients with perivascular HCC (2).

Wang *et al.* made an important contribution to the field of solitary 3–5 cm HCC by publishing in *Hepatology* (3). For cases in which the tumor diameter is smaller than 3 cm, ablation therapy has been recommended as an alternative even first-line treatment. However, the optimal treatment in 3–5 cm HCC remains disputable. The author conducted a multicenter retrospective study, comparing overall survival (OS) and disease-free survival (DFS) in patients between MWA and laparoscopic liver resection (LLR) groups. And safety parameters about two cohorts and subgroups of 3.1–4 and 4.1–5 cm HCC were analyzed.

Currently, liver transplantation, surgical resection, thermal ablation, and radiation therapy are considered curative treatments. Liver transplantation has been recognized as an optional curative treatment for HCC associated with cirrhosis and offers excellent survival outcomes in patients with single HCC smaller than 5 cm, or those with up to three nodules each smaller than 3 cm. But the application of liver transplantation is mainly limited by the severe shortage of organ donors. Surgical resection is traditionally considered as the treatment of choice for HCC because it offers the possibility of completely removing the tumor burden. Since the first description in 1992, LLR has been widely accepted and constituted as a safe option to open liver resection (OLR). In comparison, LLR owns potential advantages, such as reduced surgical stress, intraoperative blood loss, postoperative pain, length of hospital stay, and postoperative complications and mortality (4). While surgery remains the mainstay of treatment, modern treatments such as thermal ablation, neoadjuvant chemotherapy, and immune therapy have led to significant improvements in survival rates (5). Thermal ablation mainly includes RFA, MWA, and so on. Among these, MWA offers the advantages of faster heating speed, less susceptibility to heat sink effects, and is suitable for HCC.

According to China Liver Cancer Staging (CNLC) system, ablation therapy is mainly suitable for CNLC I a and suitable I b cases (for example, single tumor, diameter ≤5 cm; or 2 to 3 tumors, each maximum diameter 3 cm),

which can acquire a radical therapeutic effect. However, National Comprehensive Cancer Network (NCCN) guidelines recommend that ablation may be curative in treating solitary HCC of 3 cm or less. Lesions within 3 to 5 cm may be treated to prolong survival time using arterially directed therapies or with the combination of arterially directed therapies and ablations. Sometimes MWA is recommended to manage solitary 3–5 cm HCC in clinical practice, particularly in patients with portal hypertension or poor liver function reserve. But it was inferior to transcatheter arterial chemoembolization (TACE) combined ablation in improving patients' survival (6). Current international guidelines recommend surgical resection is suitable for early solitary HCC (≤5 cm) and without signs of portal hypertension, whereas they intend ablation is suitable for early multifocal HCC (two or three nodules ≤3 cm) and solitary small HCC without adequate liver function. Studies have reported that MWA has technical advances over RFA, including predictable ablation zone, faster ablative time, and less susceptibility to perfusion or "heat sinks" (7,8). And, analysis from the subgroup showed that MWA had better results in treating HCC >3.5 cm (9). It seems to be a more appropriate treatment for those patients with portal hypertension or poor liver reserve, even if they have HCC larger than 3 cm. However, it's still hard to say whether this treatment should be performed in patients with 3–5 cm HCC since no literature so far has separated and analyzed the OS, DFS of this group of patients.

Despite the expanding implementation of surgical and locoregional therapies worldwide, it is estimated that 50–60% of patients with HCC will eventually be treated with systemic therapies. And immunotherapies such as immune-checkpoint inhibitors (ICIs) are overturning the management of cancer (10). Ablative techniques are obtaining more and more attention for their capability of assisting with local and systemic immune effects, which makes combination tactics a promising weapon. So, the combination of ablative therapy and immunotherapy has been a subject of recent clinical and basic research. The subsequent treatment of HCC that recurs after ablation or surgical resection remains controversial. Immunotherapy plays an important role in this problem. And it is unknown whether immunotherapy affects the proliferation, migration, and invasion in patients of ablation. For instance, insufficient RFA (iRFA) could boost proliferation, migration, invasion, epithelial-mesenchymal transition (EMT), and epigenetic regulation. Bevacizumab inhibited tumor growth and angiogenesis induced by iRFA (11). Besides, local tumor ablation increases HCC immunogenicity in patients, thus promoting endogenous adjuvants release and dendritic cell activation. MWA combined with anti-programmed cell death protein-1 (anti-PD-1)/anti-cytotoxic T lymphocyte-associated antigen-4 (anti-CTLA-4) protected mice from recurrence with improved survival (12). Multiple studies have also explored the efficacy of other adjuvant immunotherapies after ablation, including the timing of ICIs administration, biomarkers that can predict therapeutic response and management of adverse events. Therefore, combing ablation with immunotherapy may be reasonable to achieve enhanced and longer anti-tumor effects and prevent solitary 3–5 cm HCC progression with improved outcomes. However, rigorous basic research and reference treatments are needed.

Though the study population of such a non-inferiority study covers a large multicenter surgery, extending to many centers, many years of follow-up, and the use of propensity score matching (PSM) analysis, there are still some biases and confounding factors in retrospective studies. Thus, it requires rigorous research in randomized controlled trials and reference treatments, which is more reliable than retrospective studies and large enough to conclude as to the advantages and disadvantages of either of the two treatment modalities, in terms of survival outcomes. For some cases with limited financial resources, the choice of LLR or MWA should also consider the increased costs of the two procedures, at least if both are equally feasible. Therefore, we believe that MWA as a first-line choice to LLR for patients with solitary 3–5 cm HCC requires further discussion and analysis.

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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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