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## Editorial

# Chemoembolization combined with radiofrequency ablation is the best option for the local treatment of early hepatocellular carcinoma?

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This study presents a valuable contribution to the field of hepatocellular carcinoma (HCC) treatment, addressing the ongoing debate surrounding the most effective nonsurgical approaches for early stage HCC.<sup>1</sup> The researchers conducted a network meta-analysis to compare the efficacy of various locoregional treatments, and their results elucidated the relative ranking of these interventions. Furthermore, chemoembolization combined with radiofrequency ablation (RFA) demonstrated superior overall survival (OS) and overall progression-free survival (PFS) compared with RFA alone.

This study indicates that combined RFA and chemoembolization therapy is the most effective option for the local treatment of early HCC<sup>1</sup>; however, acknowledging the potential shortcomings and limitations associated with this treatment approach is essential.

First, successful combined therapy relies primarily on appropriate patient selection. This treatment is not suitable for all patients with early stage HCC because of various factors

such as tumor location, size, and liver function. Tumor location is the most critical factor for determining the treatment modality, which is seldom considered in the literature, from the viewpoint of interventional radiologists. Cryoablation may be safer than radiofrequency ablation when the tumor is located near the gallbladder or bowel.<sup>2</sup> Microwave ablation, cryoablation, or external radiation therapy may be more effective than radiofrequency ablation when the tumor abutts the large vessels.<sup>3</sup> Deep-seated tumors in the Spiegel lobe may be challenging for percutaneous ablation but can be easily treated with superselective chemoembolization or radioembolization with cone-beam computed tomography guidance.<sup>4</sup> A tumor just below the heart may be more suitable for intra-arterial than for percutaneous therapy. A 3-cm tumor size is a crucial number in treatment triage, and most Asian guidelines recommend local ablation for HCCs  $\leq 3$  cm.<sup>5</sup> Similarly, radiofrequency ablation is seldom performed in patients with tumors  $>3$  cm at our institute. However, the inclusion criterion in this study was a tumor size of  $<5$  cm.<sup>1</sup> Tumors 3–5 cm in size may benefit more from the combined therapy of ablation and chemoembolization.<sup>6</sup> In particular,

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combined ablation and chemoembolization therapy may not be superior to ablation alone in patients with tumors measuring <3 cm. Most patients with Child-Pugh class A are unlikely to experience severe liver function impairment after combined ablation and chemoembolization. However, some patients with Child-Pugh class B/C may be susceptible to overtreatment.

Second, the landscape of HCC treatment is continually evolving with the introduction of novel therapies and technological advancements, including no-touch ablation and radioembolization. The data collection period of this study may not fully account for the most recent developments, and newer treatment options may have emerged that could challenge or complement the effectiveness of the combined therapy. In particular, the no-touch ablation technique has demonstrated excellent local tumor control, with a reduction in the one-year local recurrence rate by approximately one-third.<sup>7-9</sup> Additional chemoembolization is no longer required in most cases of ablation according to the operator's decision because no-touch ablation has been routinely attempted in our institutes recently. Additionally, radioembolization with curative intent for early stage HCC, which was deemed unfavorable for ablation, demonstrated excellent tumor response at a high medical cost.<sup>10</sup>

Third, the combined therapy of RFA and chemoembolization may significantly increase medical costs owing to prolonged hospitalization and increased medical resource usage.<sup>11,12</sup> Combined therapy is not fully reimbursed in some countries owing to increased medical costs and insufficient evidence of its superiority over monotherapy. The economic burden of such treatment and its impact on healthcare resources when assessing its overall value and feasibility should be considered because the current study revealed improved PFS over monotherapy, thereby decreasing the requirement of subsequent therapy and reducing overall medical costs in the long-term follow-up period.

Fourth, the combination of RFA and chemoembolization represents a complex treatment regimen that involves multiple interventions and requires expertise in both the techniques. This complexity may increase the risk of procedural complications and adverse events,<sup>13</sup> although many studies

have reported that combination treatment does not increase serious complications.<sup>1,14</sup> The study may have not fully addressed the safety profile and potential complications associated with this combined approach, thereby warranting further investigation to assess its risk-benefit ratio. Additionally, doctors may not consider manageable pain to be significant, but most patients desire to receive treatment comfortably. The combination of RFA and chemoembolization seems natural to involve more discomfort for patients than monotherapy, which may not be considered in most studies.

The study also emphasizes that cryo, microwave, and laser ablation, and proton beam therapy have similar effects on OS as RFA.<sup>1</sup> This information is valuable for clinicians when considering alternative treatment options for patients who may not be suitable candidates for a combination of chemoembolization and RFA.

However, the results revealed the relative ineffectiveness of percutaneous ethanol or acetic acid injection compared with RFA for all measured outcomes.<sup>1</sup> This finding underscores the need for caution when considering these modalities and indicates that this is not the optimal choice for early HCC treatment.

Despite the strengths of this study, some limitations should be acknowledged. First, the inclusion of only randomized trials could potentially limit the generalizability of the findings because real-world patient populations may differ. Second, the availability of studies on certain interventions may have been limited, thereby potentially affecting the robustness of the network meta-analysis. Moreover, the evolving landscape of HCC treatment should be considered because new therapies and techniques may have emerged since the data collection period.<sup>15</sup>

In conclusion, this study provides valuable insights into the comparative efficacy of various nonsurgical treatments for early HCC. These findings revealed that chemoembolization combined with RFA is the most effective option for local treatment, which may have significant clinical implications. However, further research, including head-to-head randomized trials and investigations of newer treatments, is warranted to validate and refine these findings. Clinicians should carefully consider these results when deciding on early stage

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**Abbreviations:**

HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; OS, overall survival; PFS, progression-free survival

HCC treatment and tailor their approach based on individual patient characteristics and contraindications for specific treatments.

## Conflicts of Interest

The authors have no conflicts to disclose.

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