

Surgical resection versus ablation for early hepatocellular carcinoma: the debate is still open

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Very early hepatocellular carcinoma (HCC) is usually regarded as a single tumor <2 cm in diameter without vascular invasion. BCLC stage 0 or modified UICC stage I fall into this category. Approximately, 5-10% of patients in the West and 15% of patients in Korea are diagnosed at this stage.¹⁻⁴ Very early or early HCC can be treated using ablation, surgical resection, or transplantation.⁵

In this issue of *Clinical and Molecular Hepatology*, Lee et al. evaluated the long-term outcomes of surgical resection and RFA for single HCC ≤ 3 cm in patients with well-preserved liver function (Child-Pugh class A). This multicenter retrospective study of 391 patients compared the surgical resection and RFA with a sufficient follow-up time of more than 5 years. After adjusting for covariates, the estimated cumulative overall survival was slightly higher in patients who underwent RFA than in those who underwent surgical resection (97.0% vs. 95.8% at 2 years, 92.3% vs. 89.2% at 4 years, 85.3% vs. 79.7% at 6 years, and 80.9% vs. 73.8% at 8 years, respectively) without statistical significance. However, cumulative recurrence-free survival was significantly higher in patients who underwent surgical resection than in those who underwent RFA (78.5% vs. 66.3% at 2 years, 62.1% vs. 44.5% at 4 years, 53.3% vs. 34.4% at 6 years, and 48.6% vs. 29.4% at 8 years, respectively). A subgroup analysis suggested that the difference in recurrence-free survival was statistically significant in patients without cirrhosis, whereas recurrence-free survival was comparable between patients with cirrhosis who underwent surgical resection and RFA.

The pattern of recurrence after RFA is usually categorized into intrahepatic local recurrence, intrahepatic distant recurrence, and extrahepatic distant metastasis. Incomplete ablation or tumor aggressiveness may lead to intrahepatic local recurrence.⁶ Risk factors for intrahepatic

local recurrence include larger tumor size (>3 cm), insufficient safety margin, and tumor location (adjacent to the major blood vessels).^{6,7} On the other hand, distant recurrence may result from a combination of tumor metastasis and *de novo* carcinogenesis.⁶ Risk factors for intrahepatic distant metastasis also include larger tumor size, tumor multiplicity, and high serum alpha-fetoprotein level as well as portal hypertension.^{6,7}

In the present study, a plausible reason for the difference in the recurrence-free survival rates would be that local factors, such as insufficient safety margin, are more likely to contribute to the higher recurrence of RFA than host factors, such as the presence of cirrhosis. The insufficient ablative margin of less than 5 mm is associated with higher recurrence after RFA.⁸ Tumor location is also one of the most critical factors to predict local recurrence for RFA.⁹ Unfavorable location such as periportal or subphrenic location as well as tumor size ≥ 2.0 cm are closely associated with local tumor progression in RFA.⁹ Non-subcapsular and non-perivascular tumors or tumors located in posterosuperior liver portions showed similar local tumor progression rates between RFA and laparoscopic surgical resection.¹⁰ Although the present study did not investigate the association of the tumor location and the recurrence, the authors demonstrated that recurrence-free survival was comparable for HCC ≤ 2 cm. Surgical resection provides better recurrence-free survival and comparable overall survival; however, it is accompanied by higher postoperative morbidity and longer hospital stay.¹¹ Recently, laparoscopic liver resection showed better perioperative and survival outcome compared to open liver resection.¹² Small tumors located in the anterolateral segments of the liver, laparoscopic liver resection was associated with similar complication and overall survival rates, and better recurrence-free survival compared with RFA.¹³

Underlying chronic liver disease can contribute to *the de novo* development of liver cancer after surgical resection.^{14,15} The mode of surgical resection may also affect the recurrence rate after curative resection. Anatomic resection involves the removal of a hepatic segment or subsegment, which includes tumor-bearing portal tributaries as major branches of the portal vein and hepatic artery.¹⁶ Non-anatomic resection preserves non-tumor hepatic parenchyma and offers less extensive liver resection. Anatomic resection provides better tumor control than non-anatomical resection.¹⁶ A retrospective study using propensity score matching method compared RFA and non-anatomical surgical resection for HCC ≤ 3 cm without vascular invasion. The 5-year cumulative intrahepatic distant recurrence and disease-free survival rates did not differ between patients treated using RFA and those treated using non-anatomic surgical resection (47.0% vs. 40.2%, $P=0.240$; and 48.9% vs. 54.4%, $P=0.201$, respectively).¹⁷ Non-anatomic surgical resection might not be significantly better in effectiveness compared with RFA in terms of preventing recurrence.

To decrease the intrahepatic local recurrence after RFA, new ablative techniques may play a role by improving the efficacy and size of ablation.⁶ Different ablation modes such as multi-bipolar ablation with no-touch technique or microwave ablation may lead to effective ablation and extend the indications of local ablation.⁶ Different approaches also enable safe treatment of tumors present in difficult locations. To minimize recurrence, it is important to predict tumor aggressiveness. High tumor markers, arterial peritumor enhancement, or hepatobiliary peritumoral hypointensity on magnetic resonance imaging showed the association with microvascular invasion.¹⁸ In case of HCC with a high probability of microvascular invasion, surgical resection offered better results in terms of recurrence when compared with RFA.¹⁸

Recently, a multicenter, phase 3 clinical trial comparing surgical resection and RFA for HCC ≤ 3 cm and ≤ 3 nodules was conducted.¹⁹ Interestingly, 150 patients in the surgery group and 152 patients in the RFA group were enrolled between 2009 and 2015 after confirming that all patients could be treated using either surgery or RFA. In both groups, 90% of the patients had solitary HCC. The 5-year overall survival rate was comparable between the two groups (surgery group, 74.6%; RFA group, 70.4%) ($P=0.828$). The 5-year recurrence-free survival rates were 54.7% and 50.5% in the surgery and RFA groups, respectively ($P=0.498$). Although the final report has not been published yet, balances between the modes of each treatment (e.g., application of newer ablation techniques or anatomic resection), tumor biology, or location should also be incorporated into the interpretation of results.

Presence of solitary HCC ≤ 3 cm is one of the earlier stages of HCC and can even be regarded as the easiest stage. However, tumor biology (aggressiveness), location, and hepatic reserves are ascribed to the heterogeneity of this stage. Surgical resection generally offers a lower risk of recurrence at the cost of potential complications or a longer hospital stay. RFA shows a comparable recurrence rate or overall survival rate in case of some favorably located tumors, but high recurrence rates for other unfavorably located tumors.^{1,20,21} For HCC ≥ 2 cm or located in the subphrenic or perivascular area, surgical resection would be the better option; while RFA could show similar outcomes with surgical resection for HCC < 2 cm or non-subphrenic or non-perivascular HCC. Although substantial advances have been made in both surgical resection and local ablation, the risk of recurrence should still be weighed over the risk of potential complications.

Conflict of Interest Disclosures: The authors declare no conflicts of interest pertaining to this study.

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