



# Stratification of risk of recurrence after curative-intent treatment for small hepatocellular carcinoma

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For patients with preserved liver function, tumor number and size have conventionally been main criteria for selecting optimal treatment for hepatocellular carcinoma (HCC) (1,2). Particularly for the group of patients with small ( $\leq 3$  cm) HCC, there have been aggressive discussions regarding the superiority of surgery *vs.* ablation therapies (3) because this group of patients may enjoy long-term survival with an adequate curative-intent treatment.

While several randomized controlled trials (4-6) and many observational studies have compared the efficacy of surgery and radiofrequency ablation (RFA) for HCC, no solid conclusion has been derived so far. One potential explanation for the conflicting results observed among the previous studies could be heterogeneity in tumor biology of HCC. Microvascular invasion (7,8) and tumor differentiation (9) are well-known prognostic factors for patients undergoing resection of HCC. However, because routine biopsy before RFA is not recommended due to the risk of tumor seeding or bleeding, and also intratumoral heterogeneity might cause sampling error, previous studies are missing these important histopathological data, and accordingly, there is no evidence whether or not baseline characteristics between the surgical group and RFA group are truly “equal” even in a randomized controlled trial.

Although the prognostic impact of microvascular invasion and/or tumor differentiation for solitary HCC less than 2 cm is reported to be weaker than that in larger tumors (10), presence of microvascular invasion is associated with higher risk of microscopic cancer spread which predicts early recurrence of HCC when surgeons

failed to performed systematic removal of tumor-bearing portal territory (i.e., anatomic resection) (11). Given that RFA is a locoregional therapy expecting similar oncological outcomes of partial resection (i.e., non-anatomic resection), presence of microvascular invasion could be a potential risk factor of recurrence after RFA. As such, a reliable method to predict the risk of microvascular invasion is important to select a suitable group of patients for RFA.

A recent study reported by Lee *et al.* in *Annals of Surgery* (12) tried to create a novel risk model to predict microvascular invasion of HCC. They included 4 pre-treatment factors including 2 tumor markers (AFP and PIVKA-II) and 2 magnetic resonance imaging findings (arterial peritumoral enhancement and peritumoral hypointensity on hepatobiliary phase), and confirmed excellent performance of this new risk model in an external validation cohort. When applying this new model, clear prognostic difference was observed between the patients who underwent surgery and those who received RFA when the risk score was high, while such prognostic difference was not observed when the risk score was low.

Of course, care should be paid in clinical use of the present risk model because this new model is established based on the patients with “small HCC” for the purpose of risk stratification among “small lesions”. There is no guarantee that this new score is applicable for larger HCCs. A recent similar study developing a risk prediction model for microvascular invasion using a surgical cohort within Milan criteria has shown that tumor size is an independent predictor for microvascular invasion (13). Conventionally,

tumor size (empirically approximately 5 cm) has been known to be a potent predictor of microvascular invasion among surgical population and size cut-off value of 5 cm is still used in the current version of the AJCC cancer staging manual. The novelty of the study by Lee *et al.* is that they developed a new risk stratification method for small lesions in which various treatment options including surgery, RFA, transplantations etc. are available.

Indeed, it remains challenging to adequately predict oncological risk of HCC because there are various clinical factors affecting the treatment choice and survival outcomes among patients with HCC. However, given the oncological heterogeneity of HCC, “additional risk adjustment” by using a risk prediction model would be needed to adequately compare the treatment outcomes of two or more therapeutic options even in a randomized controlled trial.

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### Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

*Ethical Statement:* The author is 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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