

# Surgical Resection or Radiofrequency Ablation for Small Hepatocellular Carcinoma

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We have read with interest the comments made by Feng et al. regarding our recent article which showed the results of our randomized controlled trial (RCT) about surgery versus radiofrequency ablation (RFA) for small hepatocellular carcinoma (SURF-Trial) [1]. A total of 301 eligible patients were randomly assigned, which 150 patients underwent surgery and 151 patients underwent RFA. Recurrence-free survival did not differ significantly between the groups: median recurrence-free survival; surgery, 3.5 years versus RFA, 3.0 years (hazard ratio, 0.92; 95% CI, 0.67–1.25;  $p = 0.58$ ). Notably, our study targeted patients with the largest HCC diameter  $\leq 3$  cm, and  $\leq 3$  HCC nodules. However, more than 90% of the patients in our study had solitary HCC nodule and approximately 65% had the largest HCC diameter  $< 2.0$  cm.

Feng et al. emphasized the importance of tumor location for considering treatment effects. They introduced a retrospective study that a single nodular HCC located at subcapsular, perivascular, and/or anterolateral segments was associated with worse survival in patients undergoing ablation than in patients undergoing laparoscopic liver resection [2]. They suggested that an RCT is probably not a good tool to reproduce the real, clinical approach to HCC and it is difficult to demonstrate any superiority of one compared with the other.

All RCTs should be understood in the context of the inclusion and exclusion criteria. The inclusion criteria of our study had tumor characteristics presented above, patient demographics, and other clinical factors. Additionally, we emphasize that all the patients were confirmed to be treatable using both surgery and RFA. Our protocol defined that before enrollment, the liver surgeons and hepatologists who performed RFA carefully assessed and reviewed HCC location and diameter in all the study participants. As such, patients who were judged not to be treated using either surgery or RFA were not included in the study. Our study did not assess the association of tumor location with survival because details of tumor location were not collected. We conducted an additional study of SURF trial. The study aimed to assess the impact of the tumor location and intervention approach (i.e., open surgery, laparoscopic surgery, and RFA) on survival. The results which will be reported soon may help in understanding the comment by Feng et al. To ensure the technical level of RFA, institutions with more than 20 RFA cases per year were included. These patients most likely had the tumor characteristics suggested by Feng et al. We conducted a prospective non-randomized study (SURF Cohort trial) [3] in parallel to the SURF RCT trial [1]. The protocol of the SURF Cohort trial also specified all the study participants were reviewed by the liver

surgeons and hepatologist, similar to the protocol of the SURF RCT trial. Interestingly, we found the imbalance of patient characteristics (e.g., larger tumors were more frequently found in the surgery group) in the SURF Cohort trial and showed that this reflected a real-world practice [3]. Indeed, a real-world nationwide registry study in Japan showed that tumor diameter from 2 cm to 3 cm was associated with worse survival in patients undergoing ablation than in patients undergoing surgery [4].

We agree that results of RCT are not always directly integrated into a real-world clinical practice. As such, our report [1] recommended carefulness when RFA is performed for HCCs in difficult locations because such tumors were excluded from our study. Nonetheless, contrary to the suggestions of Feng et al. we believe that RCT remains a good tool for assessing the effectiveness of treatments. RCTs can examine cause-effect relationships between an intervention and outcomes [5]. It should be noted that no other study design can provide this performance. We hope that a final report of our SURF-trial including the outcome of overall survival which will be reported soon helps for selecting treatments of surgery versus RFA for patients with early HCC.

### Conflict of Interest Statement

Yoshikuni Kawaguchi: lecture fees from Olympus, Conmed, Johnson and Johnson, KAKEN, Otsuka, JSS, and Chugai.

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### Author Contributions

To design and study conception: Yoshikuni Kawaguchi and Kiyoshi Hasegawa. To acquisition of data, to analysis and interpretation, and participation in revising: Yoshikuni Kawaguchi, Ryosuke Tateishi, Norihiro Kokudo, and Kiyoshi Hasegawa. Participation in drafting: Yoshikuni Kawaguchi. All authors approved the final version.