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Treatment for solitary hepatocellular carcinoma ranging from 2 and 5 cm: Is the curative effect of no-touch multibipolar radiofrequency ablation comparable to that of surgical resection?

To the Editor:

We read with great interest the recent article by Mohkam *et al.*[1] This retrospective study compared the efficacy of no-touch multibipolar radiofrequency ablation (NTM-RFA) with that of surgical resection (SR) for solitary hepatocellular carcinoma (HCC) ranging from 2 to 5 cm and concluded that both NTM-RFA and SR achieved satisfactory outcomes in terms of similar overall survival and disease-free survival. However, more patients experienced systematized recurrence and subsequently had to receive aggressive treatments in the NTM-RFA group than in the SR group. Therefore, we would like to highlight several important issues raised by this study.

Firstly, we would emphasize the impact of tumour location on the result of this research. In the present study, the prevalence of systematized recurrence was significantly higher after NTM-RFA compared to SR (7.4% *vs.* 1.9% at 12 months; 27.8% *vs.* 3.3% at 36 months; $p = 0.006$). The significant recurrence within the treated segment or in an adjacent segment less than 2 cm away from the treated tumour seems to support the opinion that the NTM-RFA procedure did not achieve complete necrosis of the tumour-bearing territory. Furthermore, in the subsequent multivariate analysis, treatment by NTM-RFA was identified as an independent risk factor for systematized recurrence (hazard ratio 8.01; 95% CI 2.14–30.00; $p = 0.002$). It can be inferred that SR may obtain a better local tumour control while NTM-RFR is less invasive leading to lower post procedure morbidity. However, with a small sample size (after inverse probability weighting adjustment, 56 cases in surgery group), less tumour control may not translate into a lower survival figure. Herein, we would stress the essential role of tumour location, which was balanced as a baseline characteristic by the authors, in the decision between these two procedures. As we know, to avoid the injury of extrahepatic vital organs and large intrahepatic vessels during the ablation procedure, the ablation procedure should be cautiously performed for the high-risk locations of HCC adjacent to extrahepatic vital organs or large intrahepatic vessels.[2] SR does not need to consider the tumour location and provides better long-term oncological outcomes for perivascular HCC than local ablation.[3] However, when the multivariate analysis of predictors of systematized recurrence was performed (in Table 4), the authors divided the location only into subcapsular, which was unscientific and increased our questioning about the location of tumours in determining the treatment modalities and in the prognosis.

Secondly, we strongly question the effect of confounding bias on the outcome of this study. With the progress in laparoscopic equipment and surgical technology, laparoscopic resection (LR) of HCC can achieve comparable oncologic outcomes with SR.[4] Meanwhile, the LR group had a shorter hospital stay, and lower postoperative morbidity,[5] which has similar advantages with NTM-RFA. Moreover, anatomical hepatectomy (AR) has been widely recognized as a treatment modality for small solitary HCC (<5 cm), which could reduce the risk of tumour recurrence and improve disease-specific survival compared to non-AR and thus improve the treatment effect.[6] Especially when the diameter of the HCC is in the range of 2–5 cm, AR should be recommended.[7] However, in this study, the operation group includes both open surgery and laparoscopic surgery. Most patients in the SR group performed open hepatectomy (46, 74.2%), which might exaggerate the advantages of NTM-RFA (lesser invasiveness) to a certain extent. We also noticed that the unadjusted SR group contained 10 (16.1%) non-AR and 52 (83.9%) AR cases in this study. Based on the small sample size, we cautiously worry whether similar results could still be obtained if the authors only compared NTM-RFA with AR or LR in this study. We think it may make more sense to compare it to the current more mainstream surgical method. Therefore, the current conclusion may be misleading to clinicians and patients.

In summary, it is not appropriate for this retrospective study to conclude that NTM-RFA achieved comparable outcomes for patients with solitary HCC ranging from 2 to 5 cm when compared with SR. Whether the location of the tumour affects the choice of treatment and whether it affects the tumour outcome remains questionable. Heterogeneous procedures in the SR group would lead to substantial bias, which should not be overlooked in such a comparative study of surgical procedures. Combined with these factors, we believe that the author's claim that NTM-RFA could be a "first-line modality of entry in the therapeutic process" for patients with solitary HCC of 2–5 cm is not established. Based on existing research, we prefer to believe that laparoscopic AR is the optimal and most beneficial treatment option for patients with well-preserved liver function and solitary HCC ranging from 2 to 5 cm. Therefore, in our opinion, the conclusion of the present study should be reviewed and interpreted cautiously.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Yuxin Zhang, Youliang Pei and Wanguang Zhang conceived the study, Yuxin Zhang and Youliang Pei written the manuscript, and Wanguang Zhang and Xiaoping Chen revised the manuscript. All authors reviewed the manuscript.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2018.10.039.

Keywords: Hepatocellular carcinoma; No-touch multibipolar radiofrequency ablation; Surgical resection.

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Reply to: "Treatment for solitary hepatocellular carcinoma ranging from 2 and 5 cm: Is the curative effect of no-touch multibipolar radiofrequency ablation comparable to that of surgical resection?"

To the Editor:

We thank Dr. Zhang and colleagues for their interest in our recently published article in the *Journal of Hepatology*.[1] The authors raised several questions regarding our findings and conclusions. We would like to address the following points.

First, Zhang *et al.* raise the importance of tumor location on results, and they claim that ablation is not appropriate for lesions adjacent to large vessels or close to extrahepatic organs. However, it has been demonstrated that no-touch multibipolar radiofrequency ablation (NTM-RFA) is much less affected by the proximity of large vessels and the so-called heat-sink effect, which makes it suitable even for hepatocellular carcinomas (HCCs) adjacent to large vessels.[2,3] Moreover, NTM-RFA is performed according to the no-touch principle[4] and could therefore be safely used for subcapsular lesions contrary to the standard monopolar RFA technique, which is associated with the risk of tumor seeding and peritoneal spread.[5] Besides, superficial lesions adjacent to extrahepatic vital organs could be safely treated by modern ablation techniques thanks to the use of artificial ascites.[6]

We disagree with the statement by Zhang *et al.* that "surgical resection does not need to consider the tumor location". In a context of underlying liver disease, it is important to consider parenchyma sparing procedures. While a superficial lesion could be safely treated by monosegmentectomy, a lesion of the same size located more deeply may require a major hepatectomy, which is associated with a higher risk of posthepatectomy liver failure. Therefore, we believe that using subcapsular (*vs.* deep) location of the lesion as an adjustment factor in the propensity score is scientifically valid.

Zhang *et al.* claim that the most mainstream treatment of HCC of 2–5 cm is represented by anatomical resection. We agree with this statement, and in our series, 84% of patients in the resection group underwent an anatomical resection. However, one should remember that many patients with HCC are at high risk of posthepatectomy liver failure, especially in the presence of portal hypertension.[7] This is why a non-anatomical resection with wider margins of 2 cm is also considered as a valid strategy, especially for superficial tumors located at the border of 2 or more adjacent segments.[8]

While it is true that the laparoscopic approach is associated with a lower morbidity and provides equivalent oncological results compared to the open approach, there is currently no evidence to support the statement made by the authors that laparoscopic resection offers a similar morbidity rate than percutaneous radiofrequency ablation, which must still be considered as a less invasive technique than laparoscopic hepatectomy.[9]

Finally, Zhang *et al.* state that our conclusion regarding the comparable outcome after surgical resection and NTM-RFA is not appropriate. However, Zhang *et al.* should recall that we clearly mentioned in our conclusion that NTM-RFA was associated with a higher rate of systematized recurrence compared to surgical resection, and our full statement was that both treatments achieved comparable long-term outcomes due to a great access to rescue therapies, such as repeat local ablation, resection, and even liver transplantation. Indeed, the vast majority of patients with intrahepatic recurrence in our series were successfully treated by a repeat curative treatment, and 1 out of 5 patients was eventually transplanted (16% after surgical resec-

Keywords: Hepatocellular carcinoma; Radiofrequency; Ablation; Hepatectomy; Local neoplasm recurrence.

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