Author’s response to reviews

Title: Comparison of open liver resection and RFA for the treatment of solitary 3-5 cm hepatocellular carcinoma: a retrospective study

Authors:

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Author’s response to reviews:

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers’ comments concerning our manuscript entitled “Comparison of open liver resection and RFA for the treatment of solitary 3-5 cm hepatocellular carcinoma”. (ID: BSUR-D-19-00482). Those comments are all valuable and very helpful for revising and improving our paper, as well as providing important guiding significance to our research. We have studied the comments carefully and have made corrections that we hope meet with approval. The revised portions are marked in bold font in the paper. The main corrections in the paper and the responses to the reviewer’s comments are as follows:

Responds to the editor’s comments:

1. Response to comment: (Clarify the study period)
Response: We are very sorry for our negligence, and we have added this information. The study period was from Jan 2011 to Dec 2015.

2. Response to comment: (Study design had to be more detailed (prospective / retrospective; criteria for case selection for resection/ablation)
Response: Considering the Editor’s suggestion, we have added the study design (retrospective) in the title and methods section; meanwhile, in the methods section, we added the selection criteria for resection or ablation. The choice between these two procedures (either liver resection or RFA) was made mainly on the basis of the location of the tumor, followed by the consideration of the preservation of hepatic function. Usually, when the shortest distance
between the edge of the target and the edge of the liver was greater than 3 cm, the cases is considered a central case in our center, and RFA is recommended.

Response to comment: (Methods and results sections should be divided by the appropriate headings)
Response: Considering the Editor’s suggestion, we have added the headings to the methods and results sections.

3. Response to comment: (Explain the technical details both for surgery (anatomical/ non-anatomical resection, vascular control, methods used for transection, etc.) and RFA (criteria for single / multiple puncture, criteria for the use of single needle / 3-pin ablation needle, use of US guidance for puncture, use of intraoperative ultrasound contrast for control, etc.))
Response: Considering the Editor’s suggestion, we have added this information. The resection is performed with the clamp method or ultrasonic knife to implement the standard resection of a liver lobe or liver segment (anatomical resection) with hemihepatic vascular occlusion, and the resected section is at least 1-2 cm from the border of the tumor (R0). There was no intraoperative radiotherapy, and portal vein intubation chemotherapy was not used. During the surgery, we applied B-mode ultrasound at the same time intra-operative localization of the resection and examination after the resection. We treated our patients with RFA using a commercially available system (Radionics, Cool-Tip System, Burlington, MA USA). All procedures were performed under general anesthesia; we located and evaluated the tumor after the ablation. All RFA cases were treated with a single needle and a single puncture on the liver surface. The duration of every RFA is determined by the size of the tumor and generally lasts at least 10 minutes. After the ablation, we used the intra-operative B-mode ultrasound to evaluate the range of ablation and the possible remaining tumor tissue, and before closing the abdomen, we again used B-mode ultrasound to inspect the whole liver to prevent the omission of lesions or incomplete ablation.

Response to comment: (Tumor location is to be defined by at least stating the criteria for centrally/peripherally located tumors.)
Response: We are very sorry for our negligence. Usually, when the shortest distance between the edge of the target and the edge of the liver was greater than 3 cm, the cases is considered a central case in our center, and RFA is recommended.

4. Response to comment: (Methods for postoperative control of the complete ablation / resection are to be stated)
Response: It is true, as Editor suggested, that if there is recurrence, we recommended the relevant treatment plan (e.g., re-resection, re-RFA, or intervention surgery) to the patients according to the basic condition of the patients, characteristics of the tumor, and other relevant factors.

5. Response to comment: (Histology after surgery (including surgical margins) and before tumor ablation (biopsy, if any) are to be included. Histologic grades (well/moderate/ poor) and tumor differentiation (low/moderate/high), are to be unified.)
Response: Considering the Editor’s suggestion, we have added the degree of tumor differentiation (low/moderate/high) to Table 1; however, histological grades
(well/moderate/poor) were not reported in our histological report system, so we cannot provide them in the present retrospective study.

6. Response to comment: (Please be more specific for the variables evaluated (eg NLR).)
Response: For the purposes of being concise, NLR has been used to refer to the neutrophil-lymphocyte ratio. We have spelled out the neutrophil-lymphocyte ratio in the patient demographics section.

7. Response to comment: (English needs revision.)
Response: We are very sorry for our negligence, and we have had our paper checked again by “American Journal Experts (https://www.aje.com/)”, a professional language editing company.

Responds to the reviewer’s comments:

Pro. Nobuhisa Akamatsu, Reviewer #1:

Thanks very much for your advice; your comments are all valuable and were very helpful for revising and improving our paper!

1. Response to comment: (Please clarify the study period.)
Response: We are very sorry for our negligence, and we have added this information. The study was conducted from Jan 2011 to Dec 2015.

2. Response to comment: (Methods section should be divided by the appropriate headings. The current form is very difficult to follow. The same was true for Results section.)
Response: Considering the Editor’s suggestion, we have added the headings to the methods and results sections.

3. Response to comment: (Please explain the details both for surgery and RFA. Do authors perform anatomical resection or partial? Single or multiple puncture for RFA?)
Response: Considering the Editor’s suggestion, we have added this information. The resection is performed with the clamp method or ultrasonic knife to implement the standard resection of a liver lobe or liver segment (anatomical resection) with hemihepatic vascular occlusion, and the resected section is at least 1-2 cm from the border of the tumor (R0). There was no intra-operative radiotherapy, and portal vein intubation chemotherapy was not used. During the surgery, we applied B-mode ultrasound at the same time intra-operative localization of the resection and examination after the resection. We treated our patients with RFA using a commercially available system (Radionics, Cool-Tip System, Burlington, MA USA). All procedures were performed under general anesthesia; we located and evaluated the tumor after the ablation. All RFA cases were treated with a single needle and a single puncture on the liver
The duration of every RFA is determined by the size of the tumor and generally lasts at least 10 minutes. After the ablation, we used the intra-operative B-mode ultrasound to evaluate the range of ablation and the possible remaining tumor tissue, and before closing the abdomen, we again used B-mode ultrasound to inspect the whole liver to prevent the omission of lesions or incomplete ablation.

Response to comment: (Please demonstrate the tumor location according to Couinaud's segment. Central/edge is not usually used for the location of HCC in the liver.)
Response: It is true as the Reviewer suggested that the segments are more precise for HCC; however, for the selection of resection or RFA, the segment is not the main factor but whether the tumor is in the center or on the edge, as stated in the methods section.

4. Response to comment: (Did author confirm the complete ablation by enhanced CT postoperatively? HCC nodules more than 3cm sometimes lead to remnant viable lesion after a single session of RFA. Did you perform additional RFA in such instances?)
Response: We have re-written this part according to the Reviewer’s suggestion: After the ablation, we used the intra-operative B-mode ultrasound to evaluate the range of ablation and the possible remaining tumor tissue, and before closing the abdomen, we again used B-mode ultrasound to inspect the whole liver to prevent the omission of lesions or incomplete ablation. In the third month after the surgery, we conducted routine enhanced CT scanning of the abdomen to further identify tumor recurrence. If there was recurrence, we recommended the relevant treatment plan (e.g., re-resection, re-RFA, or intervention surgery) to the patients according to the basic condition of the patients, characteristics of the tumor, and other relevant factors.

5. Response to comment: (How was the surgical curability? R0 resection for all cases?)
Response: The resected section was at least 1-2 cm from the border of the tumor (R0).

6. Response to comment: (Please be more specific for the variables evaluated. No spell out for NLR, nor NLR appear in the patient demographics. Histologic grades (well/moderate/poor) and tumor differentiation (low/moderate/high), please unify.)
Response: For the purposes of being concise, NLR has been used to refer to the neutrophil-lymphocyte ratio. We have spelled out the neutrophil-lymphocyte ratio in the patient demographics section. Considering the Reviewer’s suggestion, we have added the degree of tumor differentiation (low/moderate/high) in Table 1; however, the histological grades (well/moderate/poor) were not reported in our histological report system, so we cannot provide them in the present retrospective study.

7. Response to comment: (English editing is mandatory. There were too many grammatical and spelling errors.)
Response: We are very sorry for our negligence, and we have had our paper checked again by “American Journal Experts (https://www.aje.com/)”, a professional language editing company.
Pro. Elena Arabadzhieva, Reviewer #2:
Thanks very much for your advice; your comments are all valuable and were very helpful for revising and improving our paper!

1. Response to comment: (There is no information about the period of the study (the period during which the patients underwent treatment, and the period for follow-up).) 
Response: We are very sorry for our negligence, and we have added this information. The study was conducted from Jan 2011 to Dec 2015. The main outcomes of the present study were the 5-year overall survival and tumor-free survival rates, so we considered 5 years as the last follow-up time.

2. Response to comment: (The design of the study is not completely clear to me. It is written that the design of the study is retrospective but the authors declared a long-term follow-up. Is there a retrospective collection of the data, but prospective follow-up? Or, the policy of the hospital requires a postoperative observation for a 5-year period as a standard with recording the data of all patients.)
Response: We apologize for the confusion. Our present study is a retrospective study, and we retrospectively collected the follow-up data, as stated in the methods. Postoperative observation ended with death or lost of follow-up.

3. Response to comment: (The criteria for choosing between the described methods are not completely clear, too. Only localization of the tumor is mentioned. In the discussion section, it is written the liver function or presence of cirrhosis is a factor for the treatment choice, as we all know, but there are no significant differences for that in the studied groups.)
Response: The Reviewer suggested that tumor location, liver function or the presence of cirrhosis are all factors affecting the treatment choice. However, we believe that tumor location is the main factor. Our present study is a retrospective study, and there were no distinct criteria for selection when we collected the data retrospectively. We believe that future prospective RCTs will be able to better answer this question, and we are preparing such a RCT.

4. Response to comment: (It is stated that the sample is relatively large, but this cannot be concluded for sure, because we do not know what is the period of the study.)
Response: We are very sorry for our negligence, and we have added this information. The study was conducted from Jan 2011 to Dec 2015.

5. Response to comment: (A minor language revision is needed.)
Response: We are very sorry for our negligence, and we have had our paper checked again by “American Journal Experts (https://www.aje.com/)”, a professional language editing company.